

UTILITY PATENT APPLICATION TRANSMITTAL (Large Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
1073.008H

Total Pages in this Submission

TO THE ASSISTANT COMMISSIONER FOR PATENTS

Box Patent Application

Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

COMBINATORIAL DIHYDROBENZOPYRAN LIBRARY

and invented by:

Baldwin et al.If a **CONTINUATION APPLICATION**, check appropriate box and supply the requisite information:☐ Continuation ☒ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 09/295,125

Which is a:

☐ Continuation ☒ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 08/733,803

Which is a:

☐ Continuation ☐ Divisional ☒ Continuation-in-part (CIP) of prior application No.: 08/552,698Which is a X Continuation-in-part (CIP) of prior application No.: 08/ 436,120Which is a X Continuation-in-part (CIP) of prior application No.: 08/239,302

Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below
2. ☒ Specification having 196 pages and including the following:
 - a. ☒ Descriptive Title of the Invention
 - b. ☐ Cross References to Related Applications (if applicable)
 - c. ☐ Statement Regarding Federally-sponsored Research/Development (if applicable)
 - d. ☐ Reference to Microfiche Appendix (if applicable)
 - e. ☒ Background of the Invention
 - f. ☒ Brief Summary of the Invention
 - g. ☐ Brief Description of the Drawings (if drawings filed)
 - h. ☒ Detailed Description
 - i. ☒ Claim(s) as Classified Below
 - j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL (Large Entity)

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Application Elements (Continued)

3. ☐ Drawing(s) (when necessary as prescribed by 35 USC 113)
- a. ☐ Formal Number of Sheets _____
- b. ☐ Informal Number of Sheets _____
4. ☒ Oath or Declaration
- a. ☐ Newly executed (original or copy) ☐ Unexecuted
- b. ☒ Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional application only)
- c. ☐ With Power of Attorney ☐ Without Power of Attorney
- d. ☐ DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application,
see 37 C.F.R. 1.63(d)(2) and 1.33(b).
5. ☒ Incorporation By Reference (usable if Box 4b is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied
under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby
incorporated by reference therein.
6. ☐ Computer Program in Microfiche (Appendix)
7. ☐ Nucleotide and/or Amino Acid Sequence Submission (if applicable, all must be included)
- a. ☐ Paper Copy
- b. ☐ Computer Readable Copy (identical to computer copy)
- c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(B) Statement (when there is an assignee)
10. ☐ English Translation Document (if applicable)
11. ☐ Information Disclosure Statement/PTO-1449 ☐ Copies of IDS Citations
12. ☒ Preliminary Amendment
13. ☒ Acknowledgment postcard
14. ☒ Certificate of Mailing
- ☐ First Class ☒ Express Mail (Specify Label No.): EL339142833US

UTILITY PATENT APPLICATION TRANSMITTAL
(Large Entity)

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Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☒ Additional Enclosures *(please identify below):*

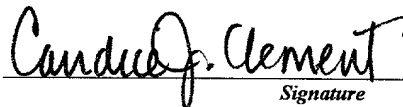
Copies of Information Disclosure Citations (3) from prior application
Copy of Assignment Document from prior application

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra	Rate	Fee
Total Claims	11	- 20 =	0	x \$18.00	\$0.00
Indep. Claims	1	- 3 =	0	x \$78.00	\$0.00
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>					\$0.00
BASIC FEE					\$760.00
OTHER FEE (specify purpose)					\$0.00
TOTAL FILING FEE					\$760.00

- ☒ A check in the amount of \$760.00 to cover the filing fee is enclosed.
- ☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. 08-1935 as described below. A duplicate copy of this sheet is enclosed.
- ☐ Charge the amount of as filing fee.
- ☒ Credit any overpayment.
- ☒ Charge any additional filing fees required under 37 C.F.R. 1.16 and 1.17.
- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).


Signature

Dated: September 8, 1999

Candice J. Clement
Reg. No. 39,946
Heslin & Rothenberg, P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600

CC:

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
37 CFR §1.10

In Re Application of: BALDWIN *et al.*

Title: COMBINATORIAL DIHYDROBENZOPYRAN LIBRARY

Attorney Docket No.: 1073.008H

"Express Mail" Mailing Label No.: EL339142833US

Date of Deposit: September 8, 1999

Enclosed herewith are:

- * Utility Patent Application Transmittal (Large Entity) - Divisional
- * Copy of Parent Patent Application (196 pages)
- * Copy of Declaration and Power of Attorney from Parent Application
- * Preliminary Amendment
- * Copies of Information Disclosure Citations (3) from Parent Application
- * Copy of Assignment Document Recorded in Prior Application
- * Check for \$760.00 (Filing Fee)
- * One Postcard

In accordance with 37 CFR §1.10, I hereby certify that this paper and the above-listed enclosures are being deposited with the U.S. Postal Service as "Express Mail Post Office to Addressee" on September 8, 1999 in an envelope addressed to:

Assistant Commissioner for Patents
Box PATENT APPLICATION
Washington, D.C. 20231

Robyn Dunlavy

(Typed or printed name of person mailing paper or fee)



(Signature of person mailing paper or fee)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Baldwin *et al.*

Atty. Dkt. No.: 1073.008H

Serial No.: Unknown
Divisional of 09/295,125
Filed: April 20, 1999
Group Art Unit: 1618
Examiner: MacMillan, K.

Title: COMBINATORIAL DIHYDROBENZOPYRAN LIBRARY

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT UNDER 37 CFR 1.121(a)

Dear Sir:

This paper is being filed contemporaneously with a filing under 37 CFR 1.53(b). Prior to examination of the accompanying divisional application, please take into consideration the following amendments and remarks.

Amendment

In the specification:

Page 1, after the title, insert

-- CROSS REFERENCE TO RELATED APPLICATIONS

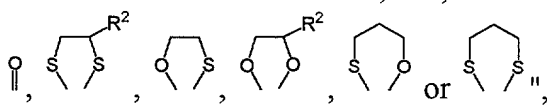
This application is a divisional of copending United States Patent Application, Serial Number 09/295,125, filed April 20, 1999, which itself is a divisional of United States Patent Application, Serial Number 08/733,803, filed October 18, 1996, which is itself a continuation in part of United States Patent Application, Serial Number 08/552,698, filed November 3, 1995, now United States Patent 5,821,130, which was itself a continuation in part of United States

Patent Application, Serial Number 08/436,120, filed May 8, 1995, now abandoned, which was itself a continuation in part of United States Patent Application, Serial Number 08/239,302, filed May 6, 1994, now abandoned. --


In the claims:

Please cancel claims 1-3 and 15-37, without prejudice.

Claim 4 (once amended), after "one of R⁶ and R⁷ is H and the other is H, OH, or

N(CH₂)₁₋₆R¹⁴R¹⁵; or R⁶ and R⁷ taken together are , or

please insert -- with the proviso that when R¹ is -OH and R² is -H, R⁶ and R⁷ are not -H and -OH

or when taken together are not  --.

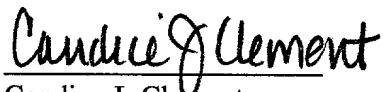
Remarks

The latest signed prior application, USSN 08/733,803 was filed as a copy of its parent application, USSN 08/552,698, along with a substantive preliminary amendment. The Declaration and Power of Attorney filed contemporaneously with USSN 08/733,803 acknowledged the amendments presented in that preliminary amendment.

The document filed contemporaneously herewith as a divisional of USSN 09/295,125 (which itself is a divisional of USSN 08/733,803) is the specification, claims and abstract of USSN 08/552,698 wherein all of the amendments presented in the aforementioned preliminary amendment have been incorporated, no other amendments have been made and no new matter has been introduced.

The parent application includes claims 1-37. Claims 1-3 and 15-37 have been canceled without prejudice herein. Applicants courteously request examination and consideration of claims 4-14 in this divisional application.

Respectfully submitted,



Candice J. Clement
Attorney for Applicants
Registration No. 39,946

Dated: September 8, 1999

HESLIN & ROTHENBERG, P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579

TITLE OF THE INVENTION

COMBINATORIAL DIHYDROBENZOPYRAN LIBRARY

BACKGROUND OF THE INVENTION

5 There is interest in methods for the synthesis
of large numbers of diverse compounds which can be
screened for various possible physiological or other
activities. Techniques have been developed in which
one adds individual units sequentially as part of the
chemical synthesis to produce all or a substantial
10 number of the possible compounds which can result
from all the different choices possible at each
sequential stage of the synthesis. For these
techniques to be successful, it is necessary for the
compounds to be amenable to methods by which one can
15 determine the structure of the compounds so made.
Brenner and Lerner (*PNAS USA* 81: 5381-83 (1992)) and
WO 93/20242, for example, describe a synthesis
wherein oligonucleotides are produced in parallel
with and are chemically linked as genetic tags to
20 oligopeptides as the compounds of interest. WO
93/06121 teaches methods for particle-based synthesis
of random oligomers wherein identification tags on
the particles are used to facilitate identification
of the oligomer sequence synthesized. A detachable
25 tagging system is described in Ohlmeyer et al., *Proc.*
Natl. Acad. Sci. USA, 90, 10922-10926, Dec. 1993.

SUMMARY OF THE INVENTION

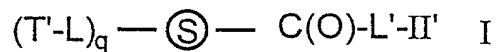
The present invention relates to combinatorial chemical libraries of compounds encoded with tags and to the use of these libraries in assays to discover biologically active compounds. The present invention also relates to libraries containing dihydrobenzopyrans and using these libraries to identify biologically active members by screening for inhibition of carbonic anhydrase isozymes. The present invention also relates to members of the library which interact (i.e., as agonists or antagonists) with α adrenergic receptors, dopamine receptors, θ -opiate receptors, and K^+ channels. In particular, the present invention also relates to members of the library which are inhibitors of carbonic anhydrase. The invention also relates to methods for their preparation, intermediates, and to methods and pharmaceutical formulations for using these dihydrobenzopyrans in the treatment of mammals, especially humans.

Because of their activity as inhibitors of carbonic anhydrase isozymes, compounds of the present invention are useful in the treatment of such diseases as glaucoma.

DETAILED DESCRIPTION OF THE INVENTION

The combinatorial libraries of the present

invention are represented by Formula I:



wherein:

\textcircled{S} is a solid support;

5 $T'-L-$ is an identifier residue;

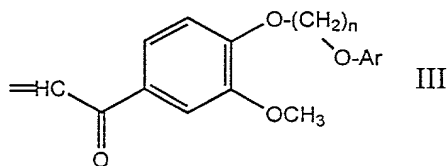
$-L'-II'$ is a compound/linker residue; and

q is 3-30.

Preferred compounds of Formula I are those

wherein:

10 $T'-L-$ is of the Formula:



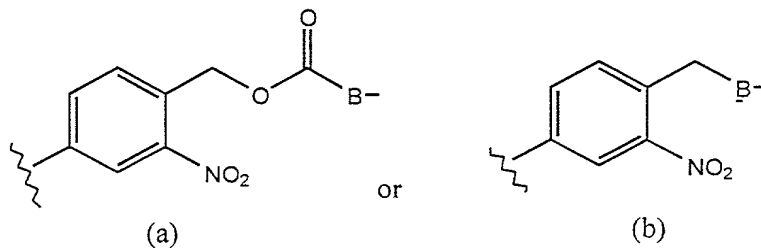
wherein

$n = 3-12$ when Ar is pentachlorophenyl and

$n = 3-6$ when Ar is 2,4,6-trichlorophenyl;

15 q is 4-12;

and $-L'-$ is

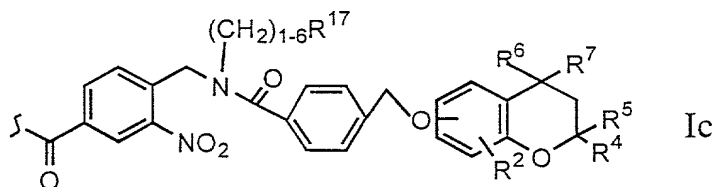
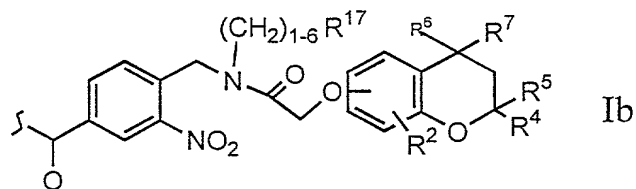
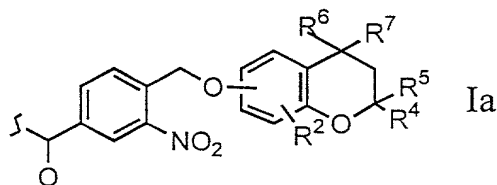


wherein the left-hand bond as shown is the point

of attachment to the solid support and the right
 hand bond is the point of attachment to the
 compound, and B is O or $N(CH_2)_{1-6}R^{17}$, with the
 proviso that in (b) when B is $N(CH_2)_{1-6}R^{17}$, the
 5 compound is attached to B through a carbonyl
 group.

Other preferred compounds of Formula I are those
 of Formulae Ia, Ib, or Ic wherein $-C(O)-L'-II'$ is:

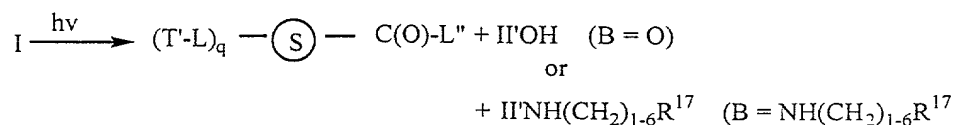
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R^{17} is H; alkyl; alkyl substituted by 1-3 alkoxy,

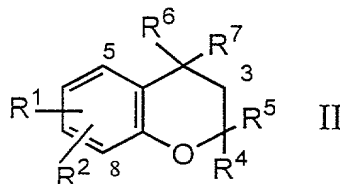
S-loweralkyl, sulfamoyl, halo,
 alkylsulphonamido, or arylsulphonamido;
 alkenyl; alkynyl; aryl; substituted aryl;
 heteroaryl; substituted heteroaryl;
 5 heterocycloalkyl; substituted
 heterocycloalkyl; diphenylmethyl; -
 $\text{CH}_2\text{NR}^{16}\text{C}(\text{O})\text{R}^{16}$; $-\text{C}(\text{O})\text{NR}^{16}\text{R}^{16}$; $-\text{CH}_2\text{OC}(\text{O})\text{R}^{16}$; or
 $-\text{CH}_2\text{SC}(\text{O})\text{R}^{16}$.

Depending on the choice of L' (see Table 1), the
 10 ligands of Formula II may be detached by photolytic,
 oxidative, or other cleavage techniques. For
 example, when $-\text{L}'-$ is (b) and B is O (or $\text{N}(\text{CH}_2)_{1-6}\text{R}^{17}$),
 photolytic detachment may be represented by:



15 wherein L'' is the residue from L' and $\text{II}'\text{OH}$ (or
 $\text{II}'\text{NH}(\text{CH}_2)_{1-6}\text{R}^{17}$) is II.

Therefore, compounds of the present invention
 are also represented by Formula II



wherein:

R^1 is OH, $O(CH_2)_{1-2}OH$, OCH_2CO_2H , CO_2H ,

$OCH_2C(O)NHCHR^{18}(CH_2)_{0-5}R^{17}$ or

$OCH_2-4-Phe-C(O)NHCHR^{18}(CH_2)_{0-5}R^{17}$

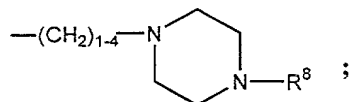
5 R^2 is H or lower alkyl;

R^3 is H, alkyl, aryl, or arylalkyl;

R^4 and R^5 are each independently H, lower alkyl, or substituted lower alkyl where the

substituents are 1-3 alkoxy, aryl,

10 substituted aryl, carboalkoxy, carboxamido, diloweralkylamido or



or R^4 and R^5 taken together are

$-(CH_2)_n-$, $-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-O-(CH_2)_3-$,

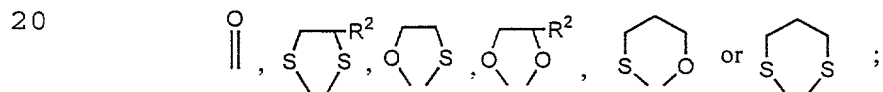
15 $-(CH_2)_2-NR^8-(CH_2)_2-$, $-CH_2-NR^8-(CH_2)_m-$,

$-(CH_2)_2CH(NHR^8)(CH_2)_2-$, $-(CH_2)_2-S(O)_{0-2}-(CH_2)_2-$, or

$-CH_2CH(N-loweralkyl)(CH_2)_2CHCH_2-$

one of R^6 and R^7 is H and the other is H, OH, or

$N(CH_2)_{1-6}R^{14}R^{15}$; or R^6 and R^7 taken together are



R^8 is H, $COOR^9$, $CONHR^{10}$, $CSNHR^{11}$, COR^{12} , SO_2R^{13} ,

lower alkyl, aryllower alkyl, heteroaryl,

or heteroaryl lower alkyl, wherein aryl is optionally substituted with 1-3

substituents selected from lower alkyl,
lower alkoxy, halo, CN, NH₂, COOH, CONH₂,
carboalkoxy, and mono- or di-lower
alkylamino and wherein heteroaryl is a
5 mono- or bicyclic heteroaromatic ring
system of 5 to 10 members including 1 to 3
heteroatoms selected from O, N, and S and
0-3 substituents selected from halo, amino,
cyano, lower alkyl, carboalkoxy, CONH₂, and
10 S-lower alkyl;
R⁹ is lower alkyl, aryl, aryl lower alkyl,
heteroaryl, aryl substituted by 1-3
substituents selected from alkyl, alkenyl,
alkoxy, methylene dioxy, and halo, or a 5
15 to 6-membered heterocyclic ring wherein the
hetero atom is O or N, wherein heteroaryl
is a heteroaromatic ring of 5 to 6 members
including 1 to 2 heteroatoms selected for
O, N, and S and 0-2 substituents selected
20 from lower alkyl, dialkylamino, lower
alkoxy, and halo;
R¹⁰ and R¹¹
are each independently lower alkyl, aryl,
aryl lower alkyl, or aryl substituted by 1-
25 3 substituents selected from lower alkyl,
halo, alkoxy, and haloalkyl;
R¹² is lower alkyl, aryl, heteroaryl, aryl lower
alkyl, heteroaryl lower alkyl, a 5- or 6-
membered heterocyclic ring containing 1-2

heteroatoms selected from O, S, and N, a 5-
 or 6-membered heterocyclic ring containing
 1-2 heteroatoms selected from O, S, and N
 lower alkyl, or aryl substituted with 1-3
 5 substituents selected from lower alkyl,
 alkoxy, halo, sulfamoyl, lower alkyl
 sulfamoyl, cyano, and phenyl;
 R¹³ is lower alkyl, aryl, or aryl substituted with
 1-3 substituents selected from lower alkyl,
 10 alkoxy, halo, CN, and haloalkyl;
 R¹⁴ is H; alkyl, alkyl substituted by 1-3 alkoxy,
 S-loweralkyl, sulfamoyl, halo,
 alkylsulphonamido, or arylsulphonamido;
 alkenyl; alkynyl; aryl; substituted aryl;
 15 heteroaryl; substituted heteroaryl;
 heterocycloalkyl; -CH₂NR¹⁶C(O)R¹⁶;
 -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or -CH₂SC(O)R¹⁶;
 R¹⁵ is H, alkyl, -C(O)X, -C(S)X, or -C(NCN)NR³R³;
 R¹⁶ is lower alkyl, substituted lower alkyl, aryl,
 20 or substituted aryl;
 R¹⁷ is H; alkyl, alkyl substituted by 1-3 alkoxy,
 2-loweralkyl sulfamoyl, halo,
 alkylsulphonamido, or arylsulphonamido;
 alkenyl; alkynyl; aryl; substituted aryl;
 25 heteroaryl; substituted heteroaryl;
 heterocycloalkyl; diphenylmethyl;
 -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or
 -CH₂SC(O)R¹⁶; or substituted
 heterocycloalkyl;

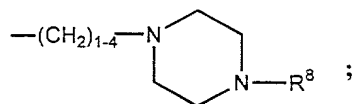
- X is alkyl, aryl, arylalkyl, O-loweralkyl, or
NR³R³
- Z is -(CH₂)₁₋₆-, optionally substituted with 1-3
lower alkyl; CHR²; Phe-CH₂-, where Phe is
5 optionally mono-substituted with halogen,
lower alkyl, or alkoxy; or
heteroarylene-(CH₂)-;
- m is 2 or 3;
- n is 4-9;
- 10 or a pharmaceutically acceptable salt thereof.

Preferred compounds of Formula II are those
wherein R¹² is sulfamoylphenyl, most preferably p-
sulfamoylphenyl.

- A preferred embodiment of the invention is
15 a compound of Formula II wherein:

- R¹ is OCH₂C(O)NHCHR¹⁸(CH₂)₀₋₅R¹⁷ or
OCH₂-4-Phe-C(O)NHCHR¹⁸(CH₂)₀₋₅R¹⁷
- R² is H or lower alkyl;
- R⁴ and R⁵ are each lower alkyl or

20



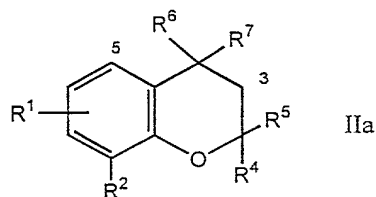
or R⁴ and R⁵ taken together are

- (CH₂)₅-, -(CH₂)₂-O-(CH₂)₂-, -(CH₂)₂-NR⁸-(CH₂)₂-,
-(CH₂)₂-CH(NHR⁸)(CH₂)₂-, -(CH₂)₂-S-(CH₂)₂-, or
-CH₂CH(NCH₃)(CH₂)₂CHCH₂-;
- 25 R⁶/R⁷ are H/OH, =O, or -S(CH₂)₂S-;

- 5
10
15
20
25
- R⁸ is H, COOR⁹, CONHR¹⁰, CSNHR¹¹, COR¹², SO₂R¹³, lower alkyl, aryl lower alkyl, heteroaryl wherein the ring members include 1 to 3 N atoms and the substituents are halo or amino, heteroaryl lower alkyl wherein heteroaryl is 6-membered and the heteroatoms are N, or aryl lower alkyl substituted with 1 substituent selected from lower alkyl, alkoxy, and halo;
- R⁹ is lower alkyl, aryl lower alkyl, aryl, tetrahydrofuranyl, tetrahydropyranyl, or aryl substituted by 1 to 2 substituents selected from lower alkyl, alkenyl, alkoxy, methylene dioxy, and halo;
- R¹⁰ and R¹¹ are each independently aryl, aryl lower alkyl, or aryl substituted by 1 substituent selected from lower alkyl, halo, alkoxy, trifluoromethyl, and pentafluoroethyl;
- R¹² is lower alkyl, aryl, aryl lower alkyl, heteroaryl lower alkyl wherein the heteroatoms are N, a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from S and N lower alkyl, or aryl substituted with 1 substituent selected from lower alkyl, alkoxy, halo, sulfamoyl, cyano, or phenyl;
- R¹³ is lower alkyl, aryl, or aryl substituted with 1 substituent selected from lower alkyl, alkoxy, and halo;

or pharmaceutically acceptable salt thereof.

Most preferred compounds of the invention are represented by the formula:



5 wherein:

R¹ is 6- or 7-OH;

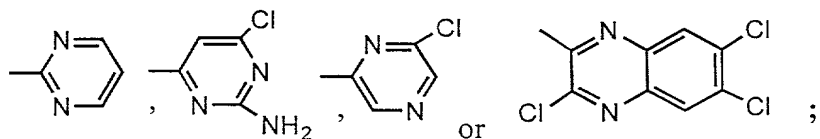
R² is H or lower alkyl;

R⁴ and R⁵ is each methyl; or R⁴ and R⁵ taken together
are -(CH₂)₅-, -(CH₂)₂-O-(CH₂)₂-,
10 -(CH₂)₂NR⁸-(CH₂)₂-, -CH₂-NR⁸-(CH₂)₃-,
-CH₂-NR⁸-(CH₂)₂-, or -(CH₂)₂-CH(NHR⁸)(CH₂)₂-;

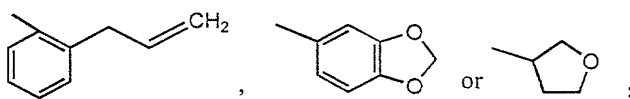
one of R⁶ and R⁷ is H and the other is OH or R⁶ and R⁷
taken together are =O or -S(CH₂)₂S-;

R⁸ is H, COOR⁹, CONHR¹⁰, CSNHR¹¹, COR¹², SO₂R¹³,

15 benzyl, -CH₂-Ph-4-F, -CH₂-pH-4-OCH₃,
-CH₂-4-Py, n-butyl, -CH₂-c-propyl,



R⁹ is i-propyl, phenyl, phenethyl, t-butyl,



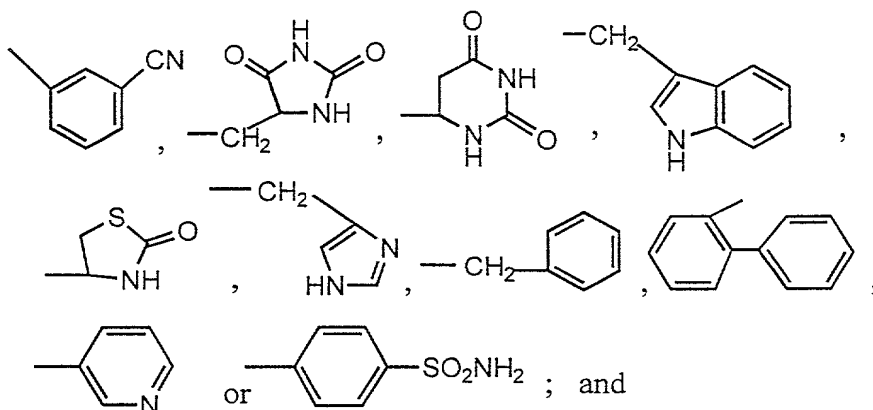
R₁₀ is phenyl, p-chlorophenyl, or

p-trifluoromethylphenyl;

R¹¹ is phenyl, benzyl, or 1-naphthyl;

 R^{12} is

5

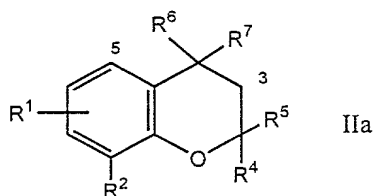


R¹³ is 1- or 2-naphthyl, phenyl, 4-chlorophenyl, 4-methylphenyl, 4-t-butylphenyl, n-butyl, or i-propyl;

or a pharmaceutically acceptable salt thereof.

10

Most preferred compounds of the invention are also represented by the formula:



wherein:

R¹ is 6- or 7-OH when R² is H;

15 R^1 is 7-OH when R^2 is CH_3 ;

R⁴ and R⁵ is each methyl; or R⁴ and R⁵ taken together

are $-(\text{CH}_2)_5-$, $-(\text{CH}_2)_2\text{-O-}(\text{CH}_2)_2-$,

$-(\text{CH}_2)_2\text{-NR}^8\text{-(CH}_2)_2-$, $-\text{CH}_2\text{-NR}^8\text{-(CH}_2)_3-$,

$-\text{CH}_2\text{-NR}^8\text{-(CH}_2)_2-$, or $-(\text{CH}_2)_2\text{-CH(NHR}^8\text{)(CH}_2)_2-$;

one of R^6 and R^7 is H and the other is OH or R^6 and R^7

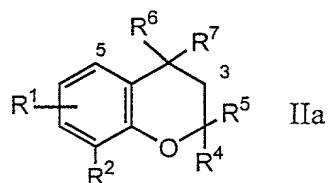
5

taken together are $=\text{O}$ or $-\text{S}(\text{CH}_2)_2\text{S-}$; and

R^8 is

		or H.

Most preferred compounds of the invention are represented by the formula:



5 wherein:

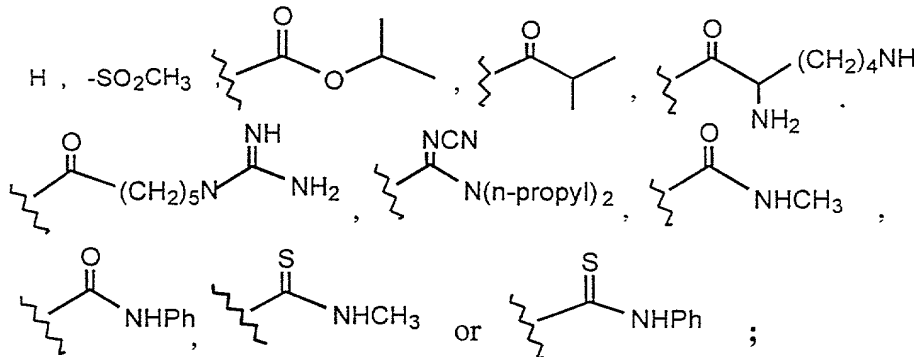
R^1 is 6- or 7-OCH₂C(O)NH(CH₂)₁₋₆R¹⁷, or 6- or 7-OCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁷ when R^2 is H;

R^1 is 7-OCH₂C(O)NH(CH₂)₁₋₆R¹⁷, or 7-OCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁷ when R^2 is CH₃;

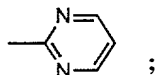
R⁴ and R⁵ is each methyl; or R⁴ and R⁵ taken together are - (CH₂)⁵-, - (CH₂)₂-O-(CH₂)₂-,
- (CH₂)₂-NR⁸-(CH₂)₂-, - (CH₂)₂-CH (NHR⁸) (CH₂)₂-,
- (CH₂)₂-S-(CH₂)₂-, or -CH₂CH (NCH₃) (CH₂)₂CHCH₂-;

5 or R⁴ is methyl and R⁵ is CH₂OCH₃ or -(CH₂)₃N(Et)₂;
one of R⁶ and R⁷ is H and the other is OH; or R⁶ and R⁷
taken together are =O or -S(CH₂)₂S-; or one
of R⁶ and R⁷ is H and the other is NAB,
where A is methyl, 2-methoxyethyl,
2-phenylethyl, 4-methoxybenzyl,
2-tetrahydro-furanylmethyl,
2(3,4-dimethoxyphenyl)ethyl, or
2,2-diphenylethyl and B is

15



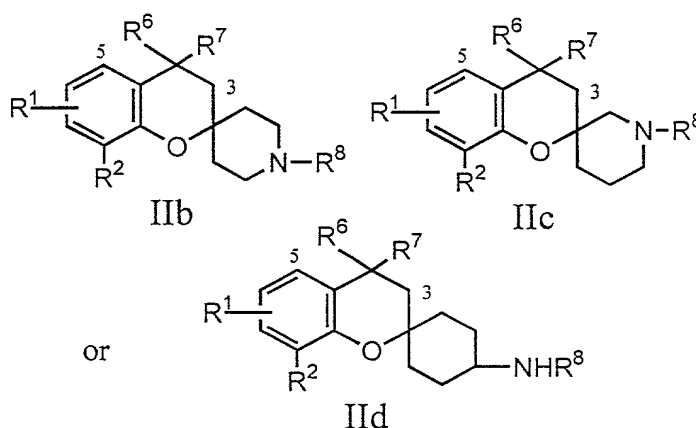
R⁸ is H, CONHCH₃, SO₂Phe, (CH₂)₃CH₃, CO(CH₂)₂CH₃, benzyl, -C(O)-(4-Phe)-SO₂NH₂, or



(CH₂)₁₋₆R¹⁴ is methyl, n-butyl, 3-methoxy-n-propyl, CH₂-
c-propyl, or -(CH₂)₁₋₃-phenyl; and
(CH₂)₁₋₆R¹⁷ is methyl, 2-methoxyethyl, 2-phenylethyl, 4-
methoxybenzyl, methyl-2-tetrahydrofuranyl,

2(3,4-dimethoxyphenyl)ethyl, or
 2,2-diphenylethyl;
 or a pharmaceutically acceptable salt thereof.

Especially preferred, as inhibitors of carbonic
 5 anhydrase, are compounds of formulae IIb, IIc, and
 IIId:



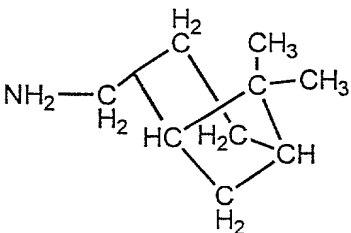
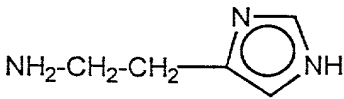
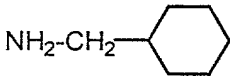
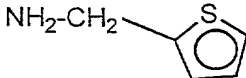
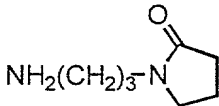
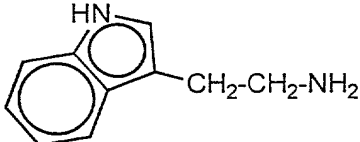
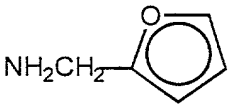
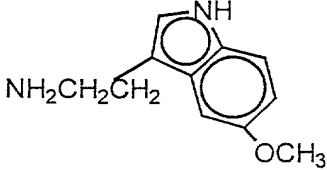
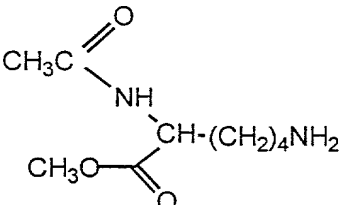
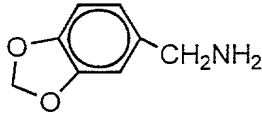
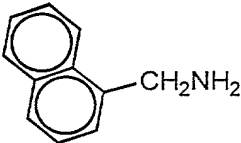
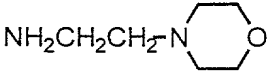
wherein:



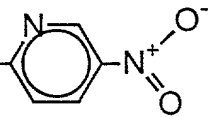
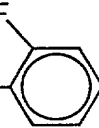

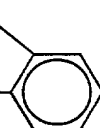

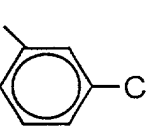

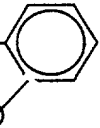

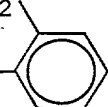
10 R^1 is 6- or 7-OH, 6- or 7-OCH₂C(O)NH(CH₂)₁₋₅R¹⁷, or
 6- or 7-OCH₂-4-Phe-C(O)NH(CH₂)₁₋₅R¹⁷;
 R^2 is H or CH₃;
 R^8 is -CO-Phe-p-SO₂NH₂; and
 R^6 and R^7 together are =O or -SCH₂CH₂S-.

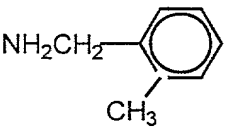
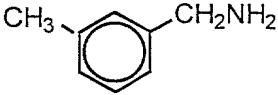
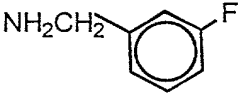
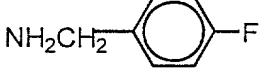
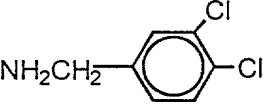
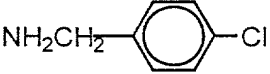
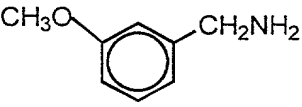
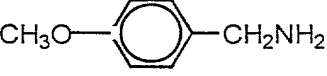
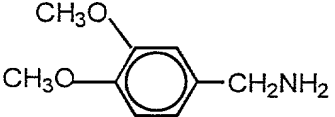
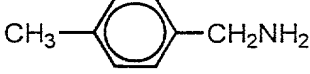
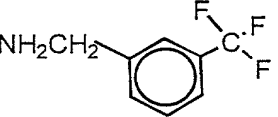
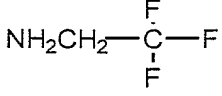
15 Most preferred of these are the following
 compounds:

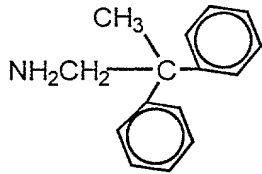
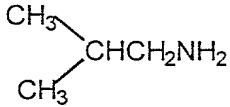
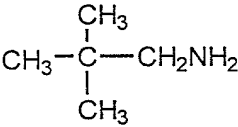
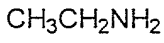
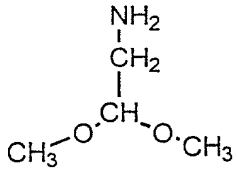
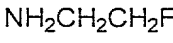
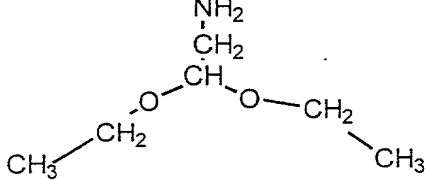
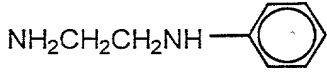
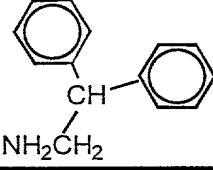
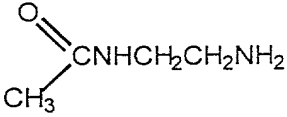
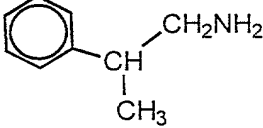
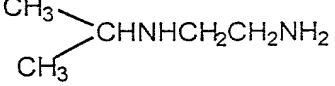
	Formula IIb	Formula IIc	Formula IIId		
R^1	7-OH	6-OH	6-OH	6-OH	7-OH
R^2	H	H	H	H	CH ₃
R^6/R^7	-O-	-SCH ₂ CH ₂ S-	-O-	-SCH ₂ CH ₂ S-	-SCH ₂ CH ₂ S-

R¹⁴ and R¹⁷ may each be any pharmacologically relevant organic radical, such as those derived by removal of H₂NCH₂- from the following compounds:

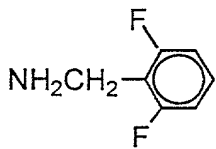
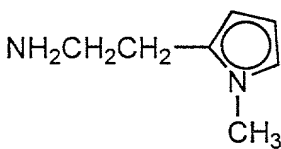
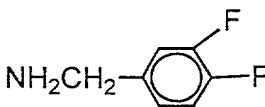
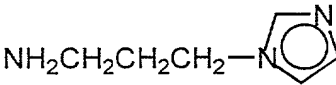
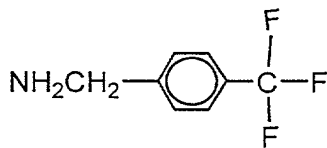
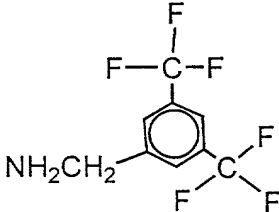
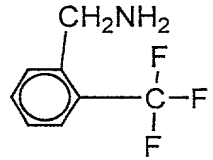
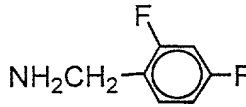
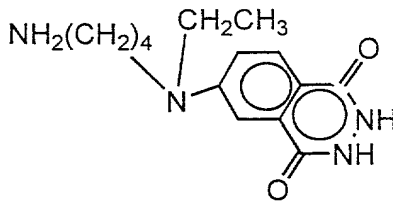
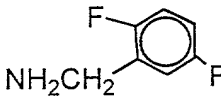
$\text{NH}_2(\text{CH}_2)_3\text{-N}$ 	$\text{NH}_2\text{CH}_2\text{-}$ 
$\text{NH}_2(\text{CH}_2)_2\text{NH-}$ 	$\text{NH}_2\text{CH}_2\text{-}$ 
$\text{NH}_2\text{CH}_2\text{-}$ 	$\text{NH}_2\text{CH}_2\text{-}$ 
$\text{NH}_2\text{CH}_2\text{CH}_2\text{-}$ 	$\text{NH}_2\text{CH}_2\text{-}$ 
$\text{NH}_2\text{CH}_2\text{-}$ 	$\text{NH}_2\text{CH}_2\text{-}$ 
$\text{NH}_2\text{CH}_2\text{-}$ 	$\text{NH}_2\text{CH}_2\text{-}$ 

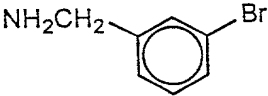
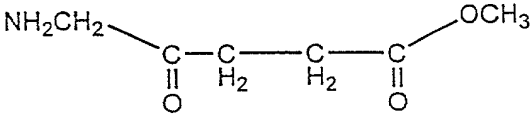
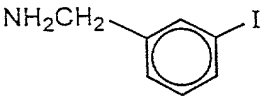
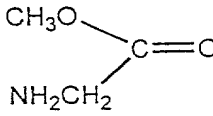
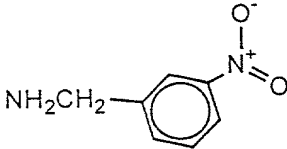
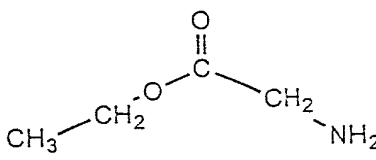
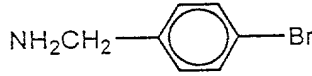
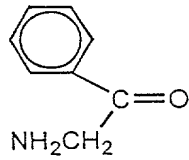
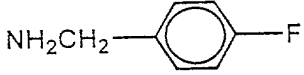
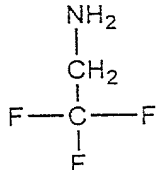
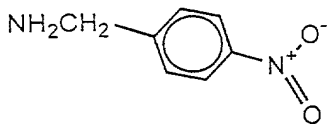
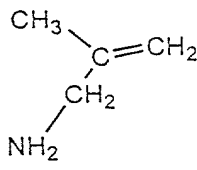
	
	
	
	
	
	


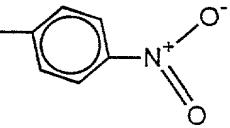

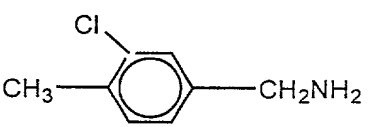
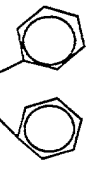
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$\text{CH}_3\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}_2$	$\text{NH}_2\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_4-\text{Br}$
$\text{CH}_3\text{OCH}_2\text{CH}_2\text{NH}_2$	$\text{NH}_2\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_4-\text{F}$
$\text{NH}_2\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_4-\text{Cl}$	$\text{NH}_2\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_4-\text{Cl}$
$\text{NH}_2\text{CH}_2\text{CH}_2-\text{C}_6\text{H}_3(\text{OCH}_3)-\text{CH}_2\text{CH}_2\text{NH}_2$	$\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CH}_2\text{CH}_2\text{NH}_2$
$\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CH}_2\text{CH}_2\text{NH}_2$	$\text{CH}_3-\text{C}_6\text{H}_4-\text{CH}_2\text{CH}_2\text{NH}_2$

$\text{NH}_2\text{CH}_2\text{C}\equiv\text{CH}$	$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{CHO}(\text{CH}_2)_3\text{NH}_2$
$\text{NH}_2\text{CH}_2\text{CH}=\text{CH}_2$	$\text{CH}_3\text{CH}_2\text{O}(\text{CH}_2)_3\text{NH}_2$
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}-(\text{CH}_2)_2\text{NH}_2 \\ \\ \text{CH}_3 \end{array}$	$\text{NH}_2(\text{CH}_2)_3-\text{C}_6\text{H}_5$
$\text{NH}_2\text{CH}_2\text{CH}_2-\text{CH} \begin{array}{l} \nearrow \text{C}_6\text{H}_5 \\ \searrow \text{C}_6\text{H}_5 \end{array}$	$\text{NH}_2(\text{CH}_2)_4-\text{C}_6\text{H}_5$
$\begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \text{CHCH}_2\text{CH}_2\text{NH}_2$	$\text{CH}_3(\text{CH}_2)_4\text{NH}_2$
$\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2$	$\text{CH}_3(\text{CH}_2)_5\text{NH}_2$

$\text{CH}_3(\text{CH}_2)_6\text{NH}_2$	
	
	
	
	
	$\text{CH}_3(\text{CH}_2)_3\text{NH}_2$

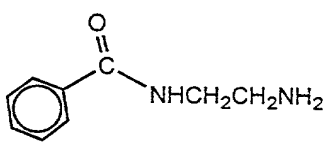
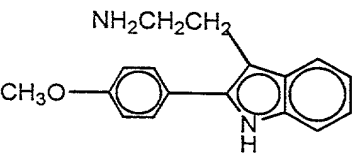
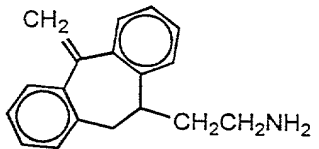
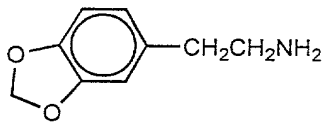
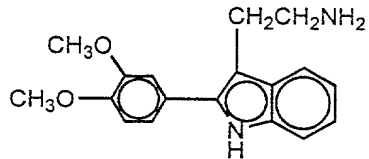
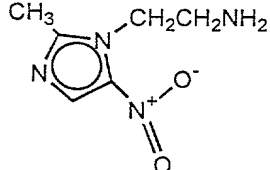
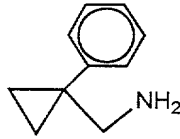
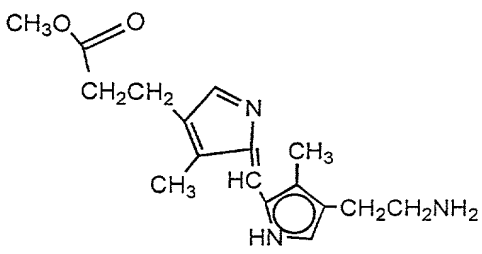
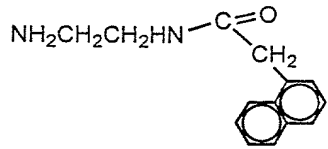
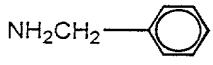
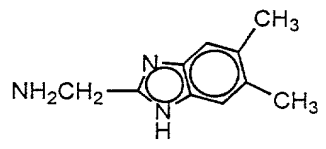
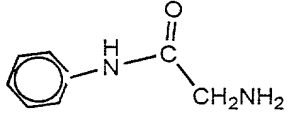
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<chem>NH2(CH2)6NS(=O)(=O)c1ccc2cc(Cl)ccc2c1</chem>	<chem>Fc1ccc2c(c1)c[nH]2CCN</chem>
<chem>NH2CH2CH2c1ccc(OCC2=CC=CC=C2)cc1</chem>	<chem>NCC(CBr)c1ccccc1</chem>
<chem>NH2CH2c1c[nH]c2ccccc12</chem>	<chem>COc1cc(CN)ccc(OC)c1</chem>
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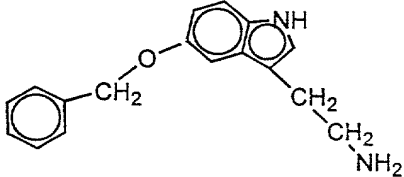
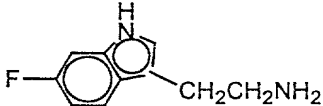
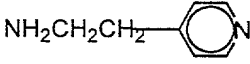
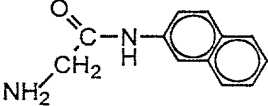
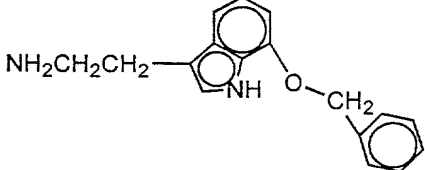
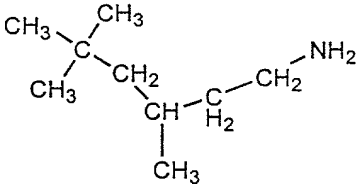
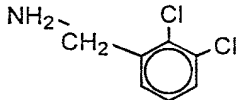
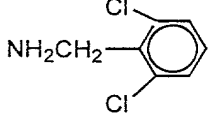
	
	
	
	
	
	

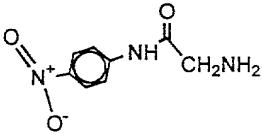
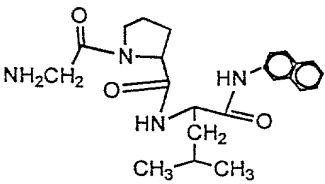
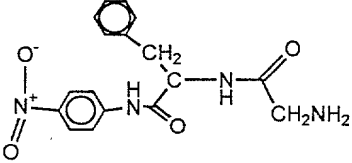
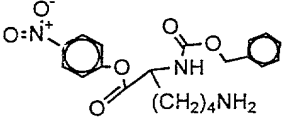
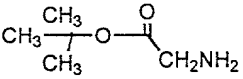
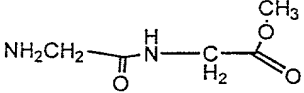
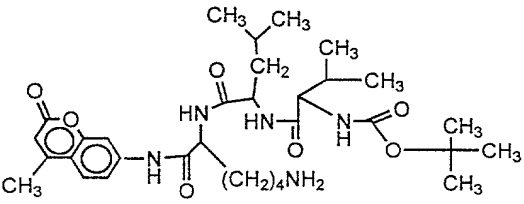
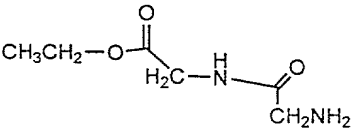
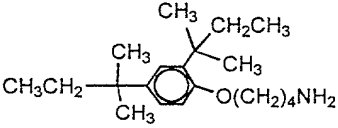
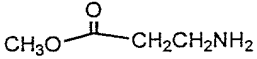
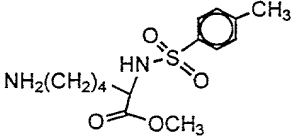
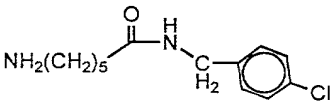
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$\text{NH}_2\text{CH}_2\text{CH}_2\text{—}$ 	$\text{CH}_3\text{CH}_2\text{O—C(=O)—CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$
$\text{CH}_3\text{CH}_2\text{SCH}_2\text{CH}_2\text{NH}_2$	$\text{NH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{—N}$ 
$\text{NH}_2\text{CH}_2\text{C} \equiv \text{CH}$	
$\text{CH}_3\text{CH}_2\text{O—C(=O)—CH}_2\text{CH}_2\text{NH}_2$	$\text{NH}_2\text{CH}_2\text{—C(F)}_2\text{—C(F)}_2\text{—C(F)}_2\text{—F}$
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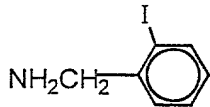
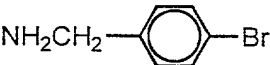
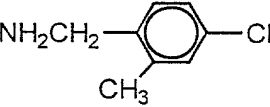
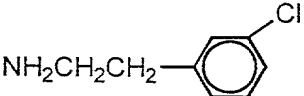
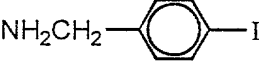
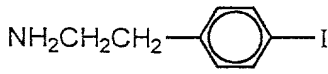
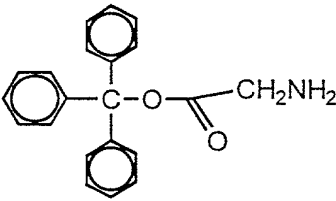
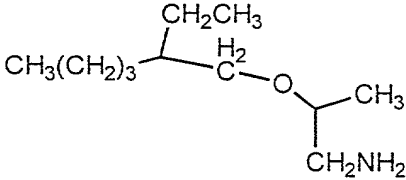
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$\text{CH}_3\text{SCH}_2\text{CH}_2\text{NH}_2$	$\text{CH}_3\text{O}-\text{C}_6\text{H}_2(\text{CH}_3\text{O})_2-\text{CH}_2\text{NH}_2$
$\text{CH}_3\text{CH}_2\text{SCH}_2\text{CH}_2\text{NH}_2$	$\text{NH}_2(\text{CH}_2)_4-\text{C}_6\text{H}_{11}$
$\text{CH}_3(\text{CH}_2)_3\text{SCH}_2\text{CH}_2\text{NH}_2$	$\text{NH}_2\text{CH}_2-\text{C}(=\text{O})-\text{NH}-\text{CH}(\text{C}_6\text{H}_5)-\text{C}(=\text{O})-\text{NH}-\text{C}_6\text{H}_5$
$\text{CH}_3\text{O}(\text{CH}_2)_3\text{NH}_2$	$\text{NH}_2\text{CH}_2-\text{C}_6\text{H}_9\text{O}$
$\text{CH}_3\text{OCH}_2\text{CH}_2\text{O}(\text{CH}_2)_3\text{NH}_2$	$\text{NH}_2\text{CH}_2-\text{C}_6\text{H}_4\text{Br}$

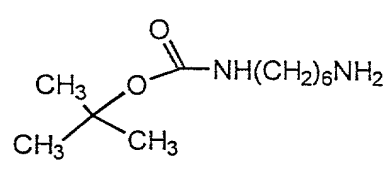
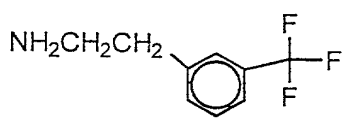
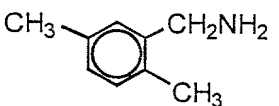
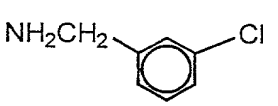
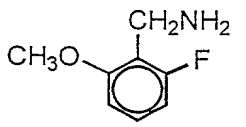
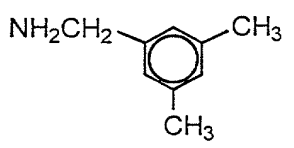
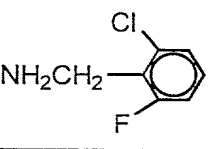
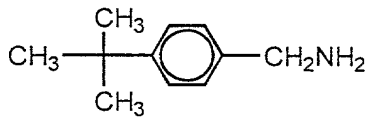
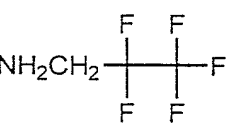
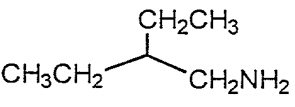
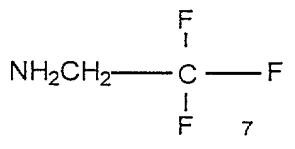
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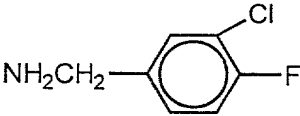
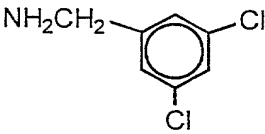
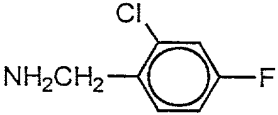
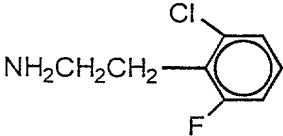
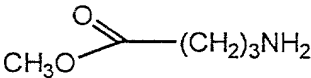
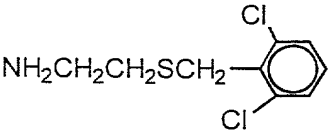
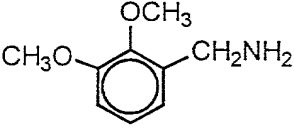
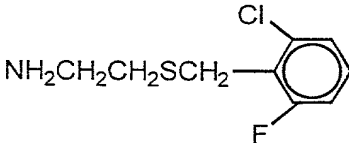
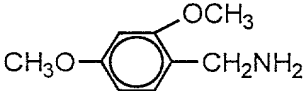
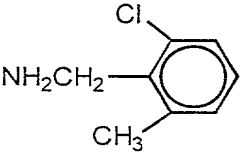
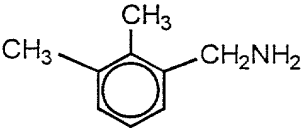
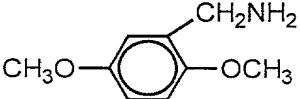
	
	
	
	
	
	

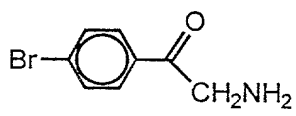
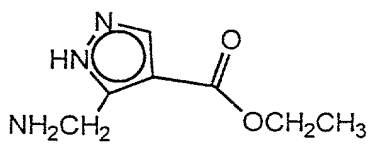
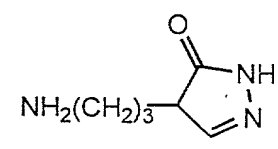
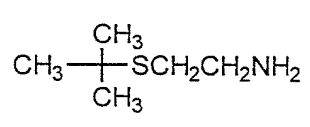
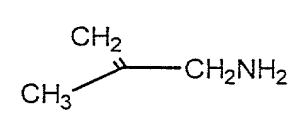
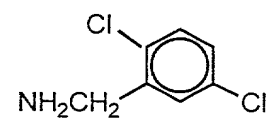
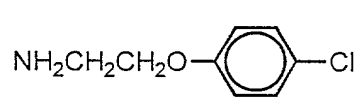
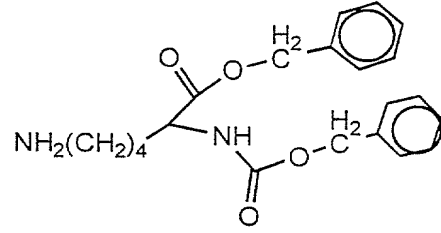
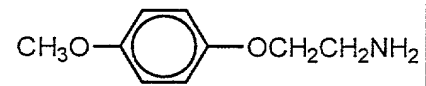
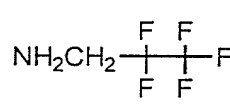
	
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$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-\text{C}_6\text{H}_4-\text{CH}_2\text{NH}_2$	
$\text{CH}_3(\text{CH}_2)_5\text{NH}_2$	
	
$\text{H}_2\text{N}(\text{CH}_2)_6-\text{CH}(\text{CH}_3)_2$	

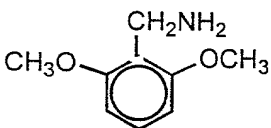
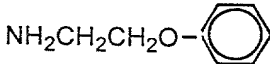
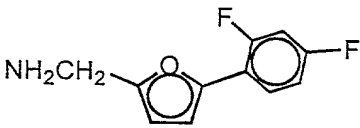
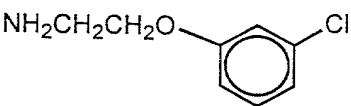
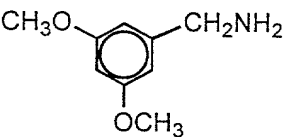
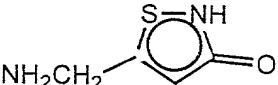
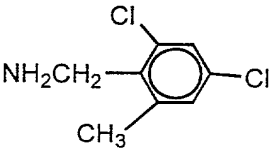
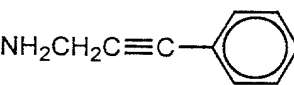
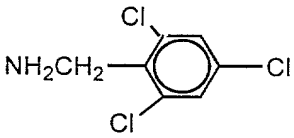
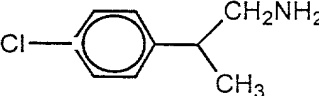
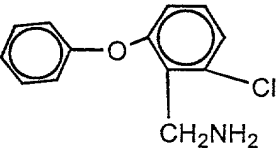
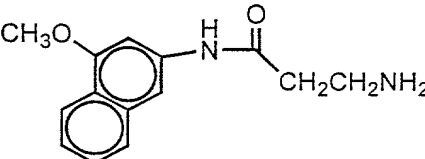
	
	
	
	
	
	

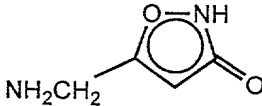
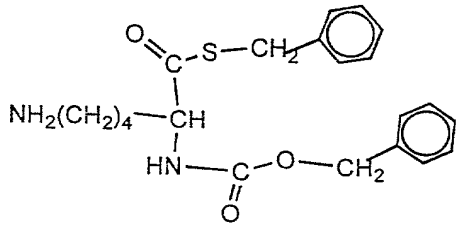
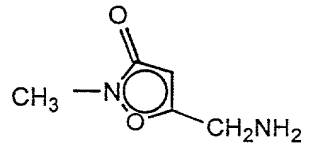
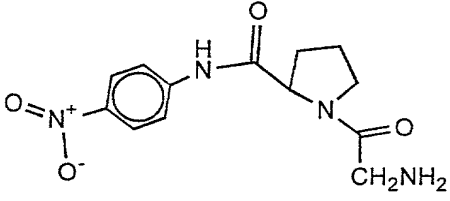
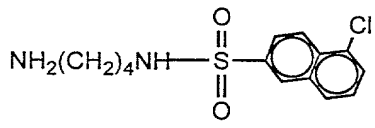
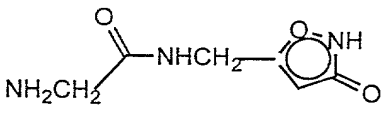
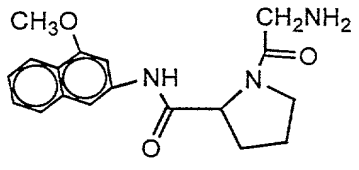
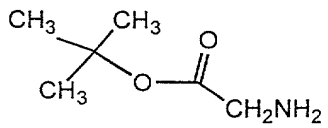
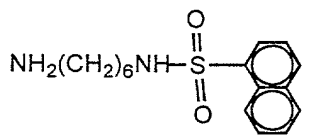
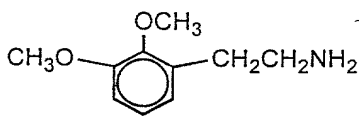
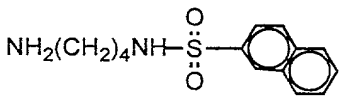
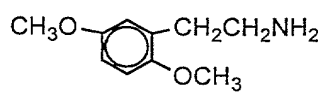
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	$\text{CH}_3(\text{CH}_2)_3\text{OCH}_2\text{CH}_2\text{NH}_2$
	
	
	$\text{CH}_3(\text{CH}_2)_3\text{CH}(\text{CH}_3)(\text{CH}_2)_6\text{O}(\text{CH}_2)_3\text{NH}_2$
	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{O}(\text{CH}_2)_3\text{NH}_2$

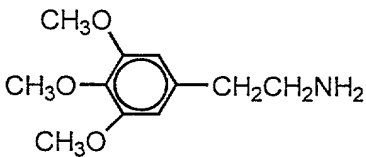
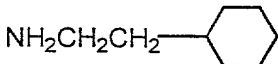
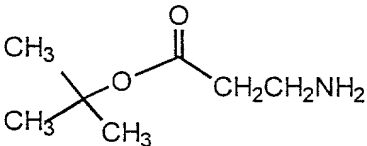
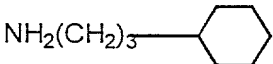
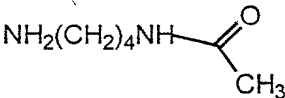
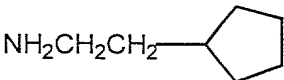
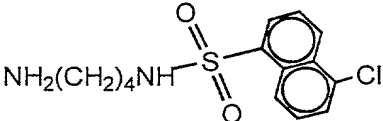
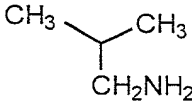
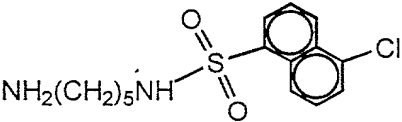
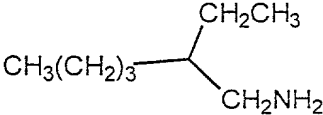
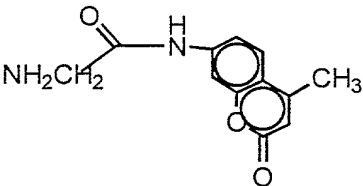
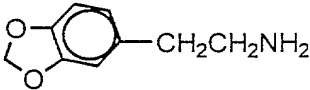
	
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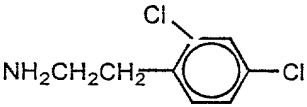
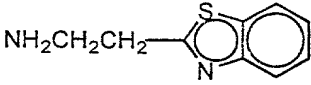
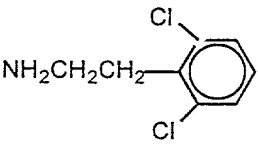
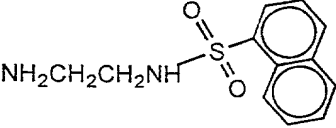
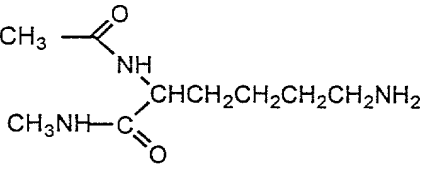
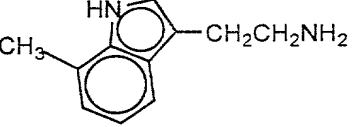
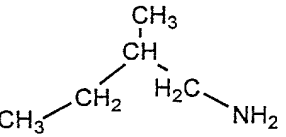
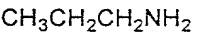
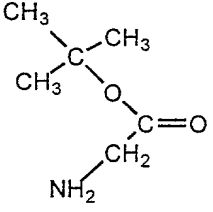
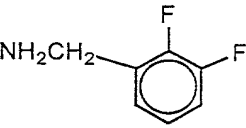
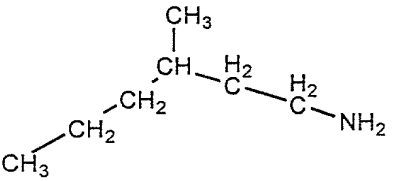
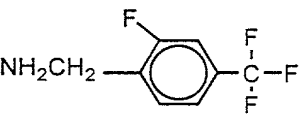
	
$\text{CH}_3\text{CH}_2\text{NH}_2$	
	
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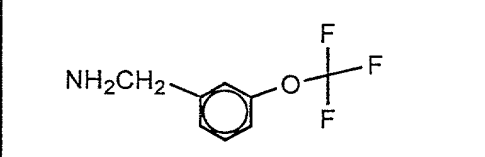
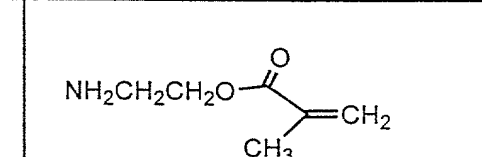
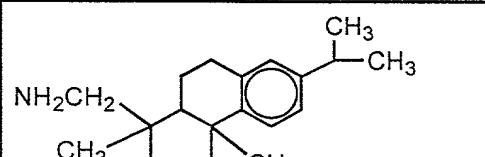
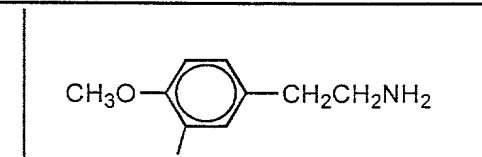
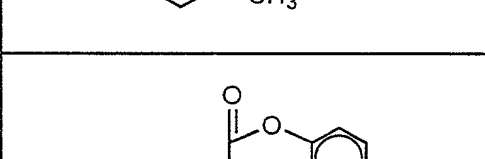
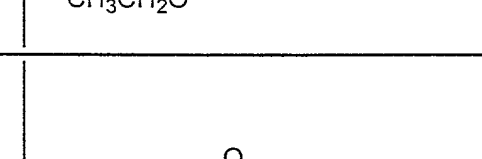
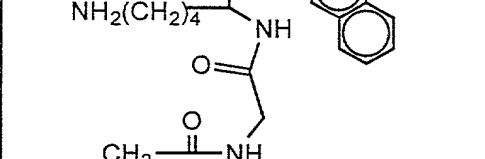
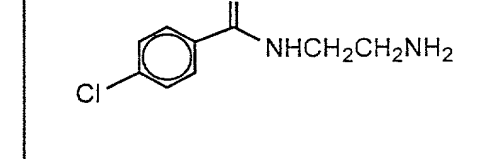
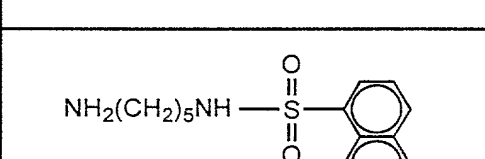
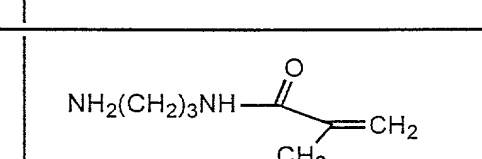
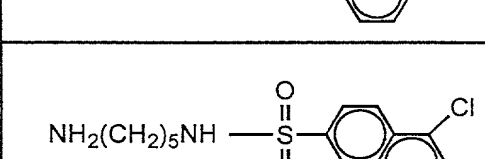
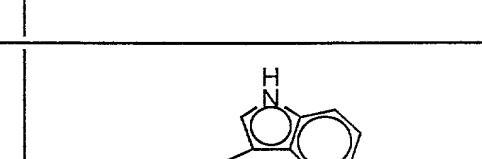
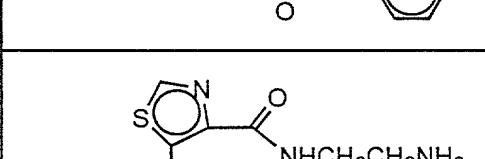
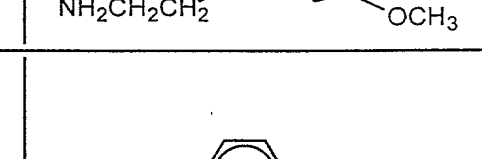
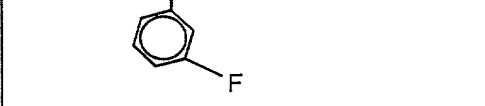
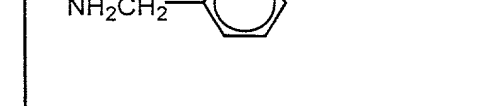
	
	
	
	
	
	

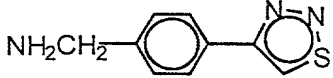
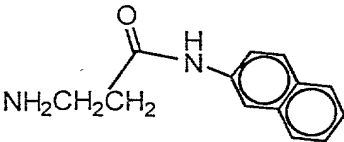
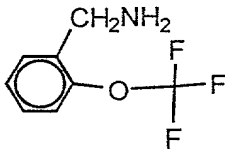
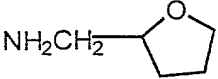
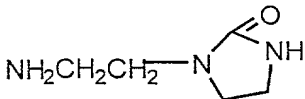
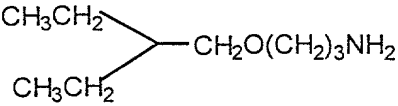
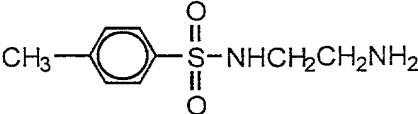
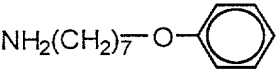
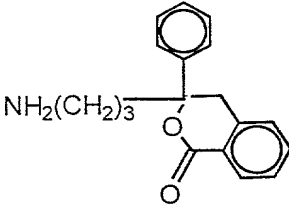
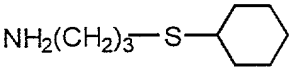
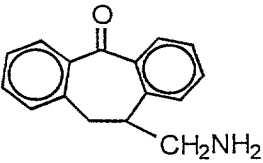
	
	
	
	
	
	

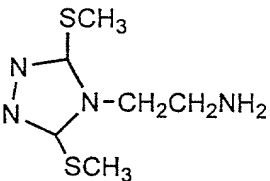
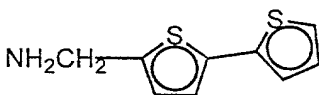
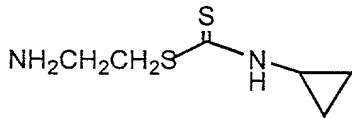
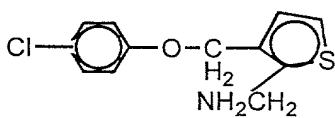
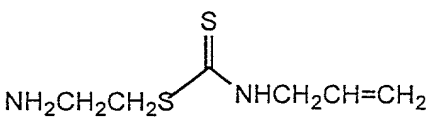
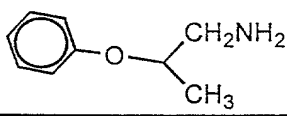
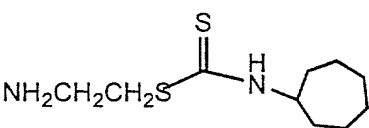
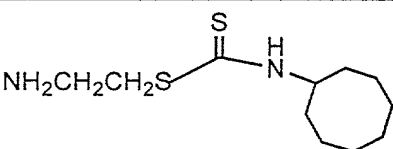
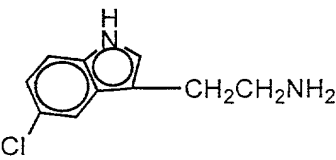
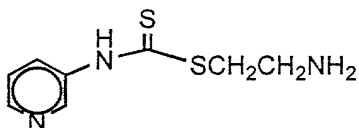
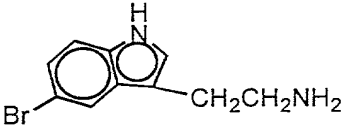
	
	
	
	
	
	

<chem>NH2CH2CH2c1ccccc1CO</chem>	<chem>NH2CH2CH2c1ccccc1Br</chem>
<chem>NH2CH2CH2c1ccc(Cl)c(Cl)c1</chem>	<chem>COc1cc(CCN)cc(OC)c1</chem>
<chem>CCOC1=CC=C(CCN)C=C1</chem>	<chem>NH2CH2CH2c1ccc(Br)cc1</chem>
<chem>NCc1cc(C(F)(F)F)c(F)c(F)c1</chem>	<chem>NCCc1cc(C(F)(F)F)c(F)cc1</chem>
<chem>NCCc1cc(C(F)(F)F)c(F)cc1</chem>	<chem>NCCc1cc(C(F)(F)F)c(F)c(F)c1</chem>
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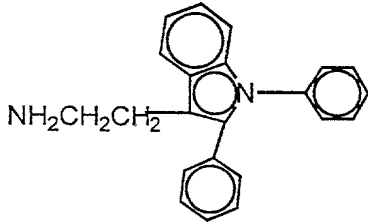
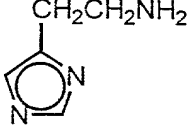
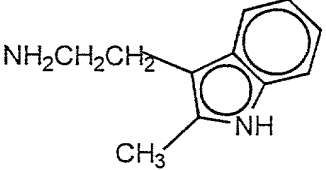
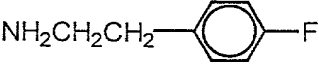
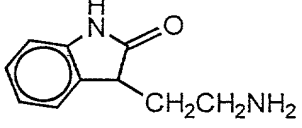
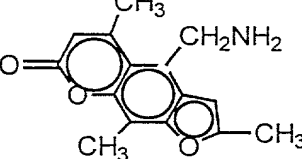
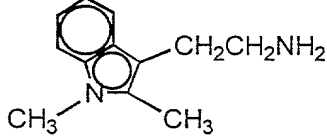
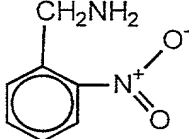
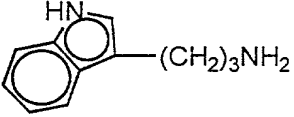
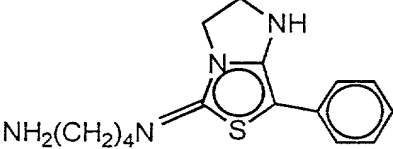
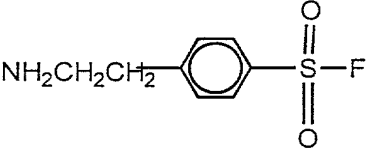
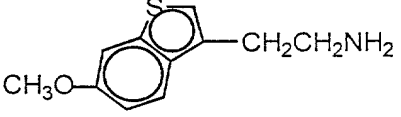
	
	
	
	
	
	

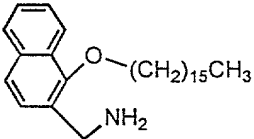
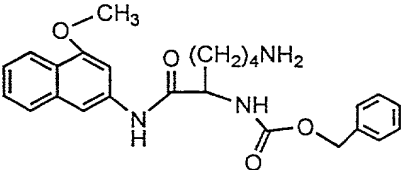
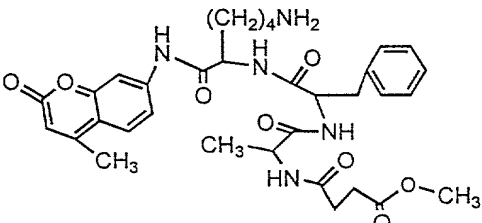
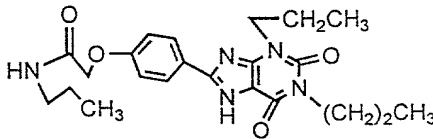
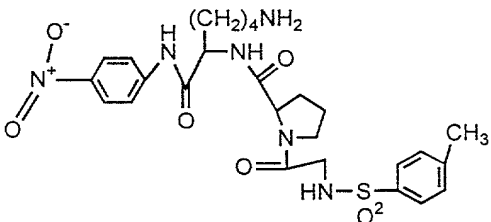
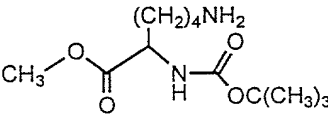
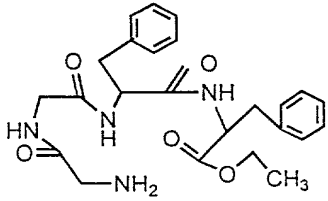
	
	
	
	
	
	
	
	

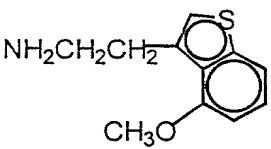
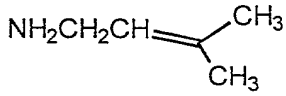
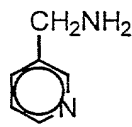
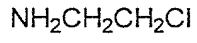
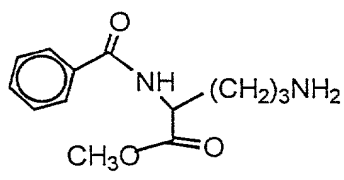
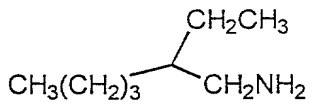
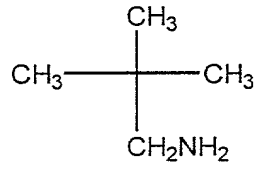
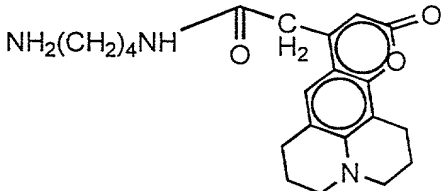
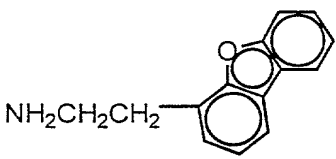
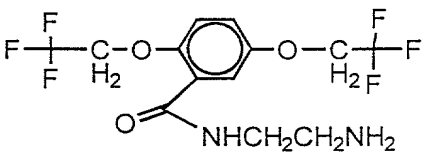
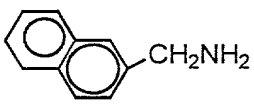
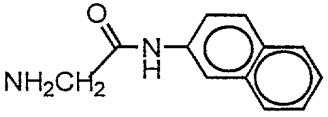
	
	$\text{CH}_3\text{O}(\text{CH}_2)_4\text{NH}_2$
	
	
	
	

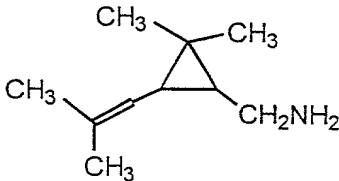
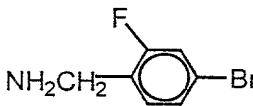
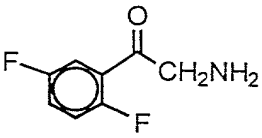
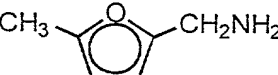
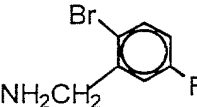
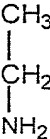
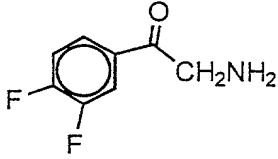
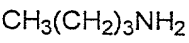
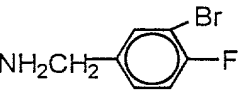
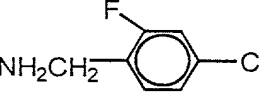
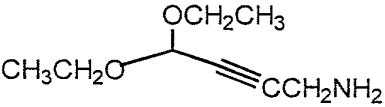
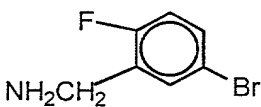
	
	
	
	$\text{CH}_3\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2)_3\text{NH}_2$
	
	

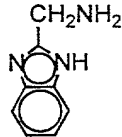
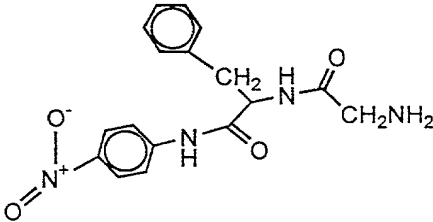
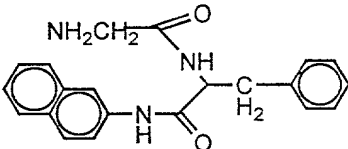
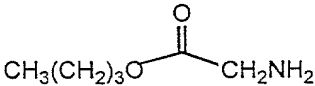
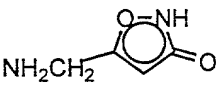
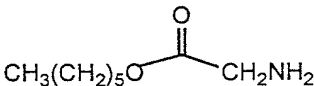
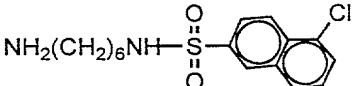
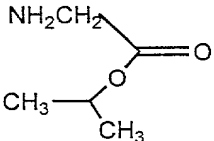
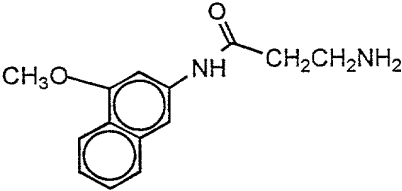
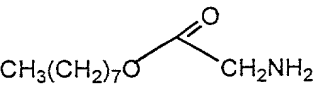
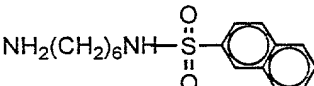
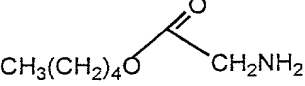
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<chem>COc1ccc(CNCCCN)c(OC)c1</chem>	<chem>NCCCNNC(=O)c1cc(F)c(F)cc1</chem>
<chem>COc1ccc(C(=O)CN)cc1OC</chem>	<chem>NCCCNNC(=O)c1nn(C)s1</chem>
<chem>NH2CH2CH2S-c1ccncc1C(F)(F)F</chem>	<chem>NH2CH2CH2Cc1ccccc1Cl</chem>
<chem>Clc1ccc(SCC2=CC=CC=C2S2)cc1</chem>	<chem>NCCCNc1ccccc1C(F)(F)F</chem>
<chem>ClC1(Cl)C=C(C1)CC(=O)NCCCN</chem>	<chem>COc1cc(CNCCCN)cc(OC)c1OC</chem>

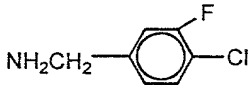
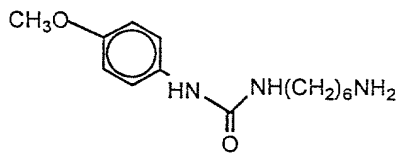
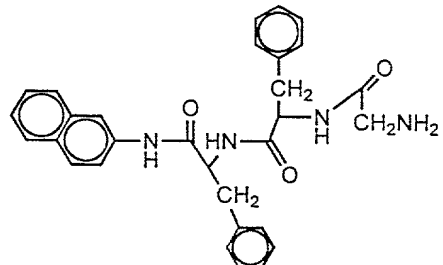
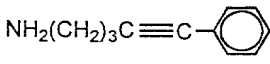
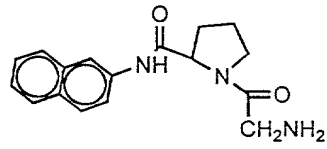
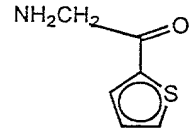
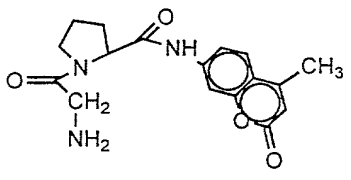
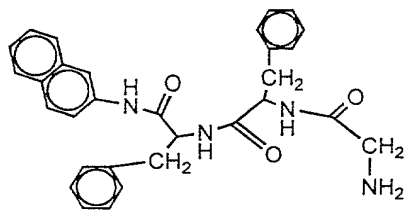
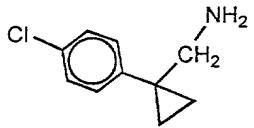
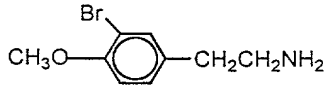
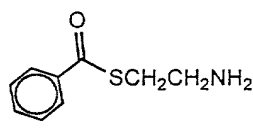
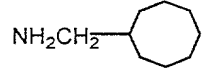
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 <chem>NCCNC(=O)c1ccccc1N(c2ccccc2)c3c[nH]c4ccccc34C</chem>	 <chem>NCCNc1ccc(F)cc1</chem>
 <chem>NCCNC(=O)c1ccccc1N(c2ccccc2)c3c[nH]c4ccccc34C=O</chem>	 <chem>NCCNC(=O)c1ccccc1N(c2ccccc2)c3cc4c(c(=O)oc5ccccc35)oc6ccccc6C</chem>
 <chem>NCCNC(=O)c1ccccc1N(c2ccccc2)c3c[nH]c4ccccc34C</chem>	 <chem>NCCNC(=O)c1ccccc1N(c2ccccc2)c3ccccc3[N+](=O)[O-]</chem>
 <chem>NCCNC(=O)c1ccccc1N(c2ccccc2)c3c[nH]c4ccccc34C</chem>	 <chem>NCCNC(=O)c1ccccc1N(c2ccccc2)c3c[nH]c4ccccc34C</chem>
 <chem>NCCNC(=O)c1ccccc1N(c2ccccc2)c3c[nH]c4ccccc34C</chem>	 <chem>NCCNC(=O)c1ccccc1N(c2ccccc2)c3c[nH]c4ccccc34C</chem>

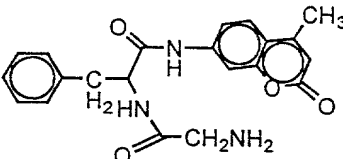
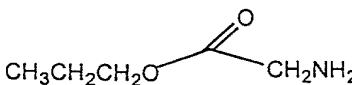
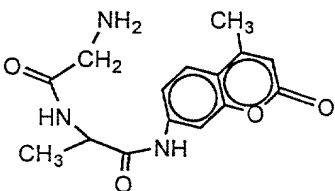
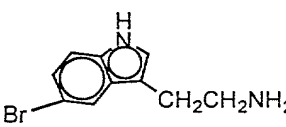
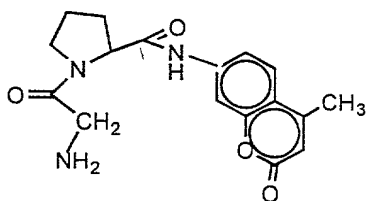
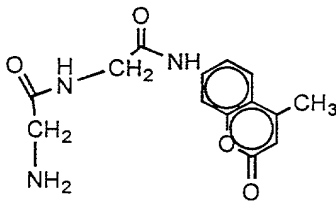
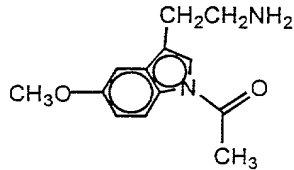
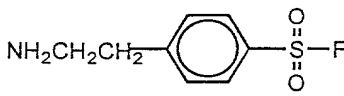
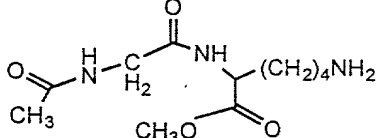
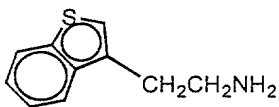
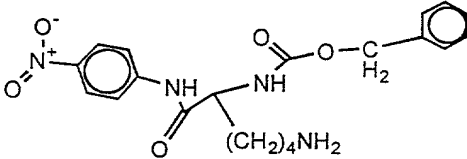
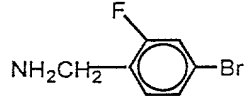
	
$\text{CH}_3(\text{CH}_2)_7\text{CHCH}(\text{CH}_2)_8\text{NH}_2$	$\text{CH}_3(\text{CH}_2)_9\text{NH}_2$
$\text{CH}_3(\text{CH}_2)_{12}\text{NH}_2$	
$\text{CH}_3(\text{CH}_2)_{15}\text{NH}_2$	
$\text{CH}_3(\text{CH}_2)_{17}\text{NH}_2$	
	

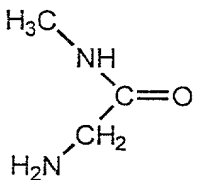
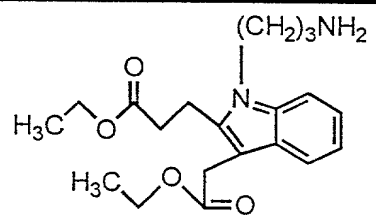
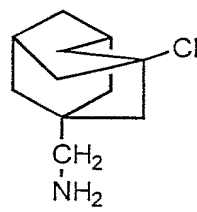
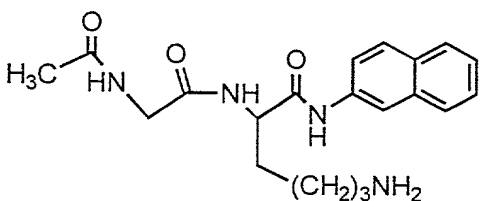
	
	
	
	
	
	

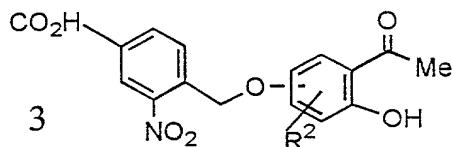
	
	
	
	
	
	

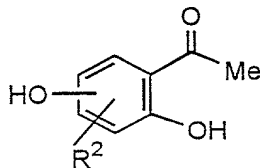
$\text{CH}_3(\text{CH}_2)_{11}\text{NH}_2$	
	
	

One embodiment of the invention is the use of the combinatorial library of Formula I in assays to discover biologically active compounds (ligands) of Formula II. Thus, an aspect of the invention is a method of identifying a compound having a desired characteristic which comprises synthesizing a combinatorial library of Formula I and testing the compounds of Formula I and the ligands of Formula II, either attached to the solid support or detached therefrom, in an assay which identifies compounds having the desired characteristic. A further embodiment of the invention is determining the structure of any compound so identified.

Another embodiment of the invention is a process for preparing a compound of the formula:

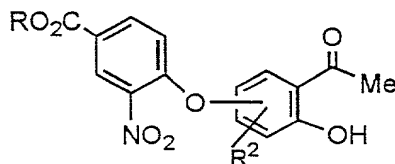


where R^2 is H or lower alkyl, which comprises a) reacting allyl or methyl 4-(hydroxymethyl)-3-nitrobenzoate with a compound of the formula:



in the presence of triphenylphosphine, toluene, and

DEAD and stirring the mixture at room temperature to produce



where R is allyl or methyl, and b) when R is allyl reacting said compound with methylene chloride, tetrakis(triphenylphosphine) palladium(0), and pyrrolidine and stirring the mixture at 0°C, or when R is methyl reacting said compound with dilute NaOH and THF and stirring the mixture at 0°C.

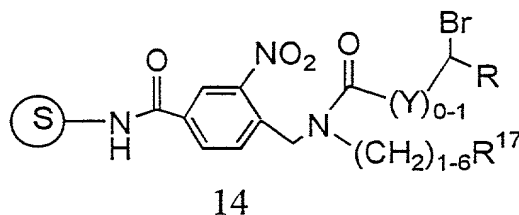
For this reaction, R=allyl is preferable to the t-butyl or methyl esters since the milder conditions would not induce aldol type condensation of the acetophenone portion of the molecule.

Another embodiment of the invention is a method for identifying compounds that are inhibitors of carbonic anhydrase which comprises preparing a mixture of 20-300 pmol test compound and aqueous solutions (total volume; 25-100, preferably about 50, μ L) of 0.03-0.12, preferably about 0.06, μ M carbonic anhydrase and 0.04-0.16, preferably about 0.08, μ M dansylamide, exposing said mixture to U.V. (preferably 274 nm) light, and determining the amount of emitted U.V. (preferably 454 nm) light.

Another embodiment of the invention is a method

for identifying compounds that are enzyme inhibitors which is a lawn assay which comprises contacting a colloidal matrix containing enzyme, which matrix has embedded therein a mono-layer of solid supports with attached ligands, with a layer of fluorogenic substrate-containing material, eluting said ligands by exposure to U.V. light, and detecting zones of inhibition in the colloidal matrix produced thereby. A preferred such lawn assay comprises contacting an agarose matrix containing bovine carbonic anhydrase with a fluorescein diacetate-containing layer of agarose.

Another embodiment of the invention is a compound of the formula:



wherein:

(S) is a solid support;

R is H or alkyl;

R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;

R¹⁷ is H; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido;

alkenyl; alkynyl; aryl; substituted aryl;
heteroaryl; substituted heteroaryl;
heterocycloalkyl; $-\text{CH}_2\text{NR}^{16}\text{C}(\text{O})\text{R}^{16}$;
 $-\text{C}(\text{O})\text{NR}^{16}\text{R}^{16}$; $-\text{CH}_2\text{OC}(\text{O})\text{R}^{16}$; OR $-\text{CH}_2\text{SC}(\text{O})\text{R}^{16}$;

5 and
Y is aryl or heteroaryl.

10 Compounds of formula 14 are useful as
intermediates in the construction of combinatorial
libraries and are especially useful in automated or
batch mode syntheses thereof.

Definitions

The following abbreviations have the indicated
meaning:

15 Boc = t-butyloxycarbonyl
 c- = cyclo
 DEAD = diethylazodicarboxylate
 DBU = 1,8-diazabicyclo[5,4,0]undec-7-
 ene
20 DCM = dichloromethane = methylene
 chloride
 DIC = diisopropylcarbodiimide
 DMAP = 4-N,N-dimethylaminopyridine
 DMF = N,N-dimethylformamide
 DMSO = dimethyl sulfoxide
25 DVB = 1,4-divinylbenzene
 EDT = 1,2-ethanedithiol
 equiv. = equivalent
 Et = ethyl

	FACS	=	fluorescence activated cell sorting
	Fmoc	=	9-fluorenylmethoxycarbonyl
	GC	=	gas chromatography
5	HOBt	=	N-hydroxybenzotriazole
	hr	=	hour, hours
	im	=	imidazole
	in	=	indole
	m-	=	meta
10	Me	=	methyl
	Mtr	=	4-methoxy-2,3,6- trimethylbenzenesulfonyl
	n-	=	normal
	Naph	=	naphthyl
15	p-	=	para
	PEG	=	polyethylene glycol
	Ph	=	phenyl
	Phe	=	phenylene
	Pmc	=	2,2,5,7,8-pentamethylchroman-6- sulfamoyl
20	Py	=	pyridyl
	r.t.	=	room temperature
	sat'd	=	saturated
	s-	=	secondary
25	t-	=	tertiary
	t-Boc	=	t-butyloxycarbonyl
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran

"Alkyl" is intended to include linear, branched,

or cyclic structures and combinations thereof of from 1 to 20 carbon atoms. "Lower alkyl" includes alkyl groups of from 1 to 8 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, octyl, c-propyl, c-butyl and the like. "Lower cycloalkyl" includes cycloalkyl groups of from 3 to 8 carbon atoms. Examples of lower cycloalkyl groups include c-propyl, c-butyl, c-pentyl, 2-methylcyclopropyl, cyclopropylmethyl, and the like.

"Alkenyl" is C₂-C₆ alkenyl of a linear, branched, or cyclic (C₅-C₆) configuration and combinations thereof. Examples of alkenyl groups include allyl, isopropenyl, pentenyl, hexenyl, c-hexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" is C₂-C₆ alkynyl of a linear, branched, or cyclic (C₅-C₆) configuration and combinations thereof. Examples of alkynyl groups include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl, isopropynyl, pentynyl, hexynyl, c-hexynyl, 1-propynyl, 2-butyne, 2-methyl-2-butyne, and the like.

"Alkoxy" means alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy,

cyclohexyloxy, and the like.

"Substituted loweralkyl" means lower alkyl substituted with 1-3 alkoxy, carboalkoxy, carboxamido, di-loweralkylamino, aryl, substituted aryl, heteroaryl.

"Aryl" means phenyl or naphthyl.

"Substituted aryl" means aryl substituted with 1-3 halo, loweralkyl, alkoxy, aryl, S-loweralkyl, alkylsulphonamido, arylsulphonamido, or sulfamoyl.

"Heteroaryl" means a 5 or 6 membered aromatic ring containing 1-3 hetero atoms selected from O, N, and S.

"Substituted heteroaryl" means heteroaryl substituted with 1-3 halo, loweralkyl, alkoxy, aryl, S-loweralkyl, alkylsulphonamido, arylsulphonamido, or sulfamoyl.

"Heterocycloalkyl" means lower cycloalkyl containing 1-3 hetero atoms selected from O, N, and S.

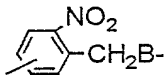
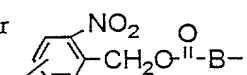
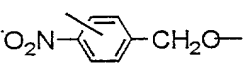
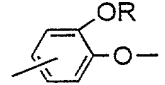
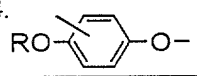
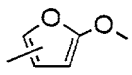
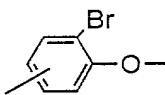
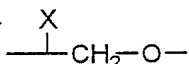
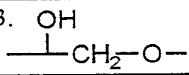
Halogen includes F, Cl, Br, and I.

L and L' are depicted in Table 1, which also shows cleavage reagents. In designing a synthetic scheme, L and L' are chosen such that they are

orthogonally reactive; i.e., they must allow for removal of either T or II(where $T = T' - OH$) without removal of the other since simultaneous cleavage of both T and II from the solid support is

5 disadvantageous. In the structures as shown, the left-hand bond is the point of attachment to the solid support and the right-hand bond is the point of attachment to either T or II.

TABLE 1
LINKER GROUPS

LINKER GROUP	CLEAVAGE REAGENT
1.  or 	hν
2. 	hν
3. 	Ce(NH ₄) ₂ (NO ₃) ₆
4. 	Ce(NH ₄) ₂ (NO ₃) ₆
5. -CH=CH(CH ₂) ₂ -	O ₃ , OsO ₄ / IO ₄ ⁻ or KMnO ₄
6. -CH=CHCH ₂ -	O ₃ , OsO ₄ / IO ₄ ⁻ or KMnO ₄
7. -CH ₂ CH=CH-	O ₃ , OsO ₄ / IO ₄ ⁻ or KMnO ₄
8. 	1) O ₂ OR Br ₂ , MeOH 2) H ₃ O ⁺
9. -CH=CHCH ₂ O-	(Ph ₃ P) ₃ RhCl(H)
10. 	Li, Mg or BuLi
11. -S-CH ₂ -O-	Hg ⁺²
12. 	Zn or Mg
13. 	Oxidation, <i>e.g.</i> , Pb(OAc) ₄ or H ₅ IO ₆

R = H or lower alkyl

X = electron withdrawing group such as Br, Cl and I.

The tags of this invention, T, are chemical entities which possess several properties: they must be detachable from the solid supports, preferably by photolysis or oxidation; they must be individually
5 differentiable, and preferably separable; they must be stable under the synthetic conditions; they must be capable of being detected at very low concentrations, e.g., 10^{-13} to 10^{-9} mole; they should be identifiable with readily-available equipment
10 which does not require sophisticated technical capabilities to operate; and they should be relatively economical. The tags may be structurally related or unrelated, e.g., a homologous series, repetitive functional groups, related members of the
15 Periodic Chart, different isotopes, combinations thereof, and the like. At the end of the combinatorial synthesis, to each solid support, there will usually be attached at least 0.01 femtomol, usually 0.001-50 pmol, of each tag. The tags may be
20 aliphatic, alicyclic, aromatic, heterocyclic, or combinations thereof. Distinguishing features may be the number of repetitive units, such as methylene groups in an alkyl moiety; alkyleneoxy groups in a polyalkyleneoxy moiety; halo groups in a polyhalo
25 compound; α -and/or β -substituted ethylene groups where the substituents may be alkyl groups, oxy, carboxy, amino, halo, or the like; isotopes; etc.

The materials upon which the combinatorial syntheses of the invention are performed are referred

to as solid supports, beads, and resins. These terms are intended to include:

a) beads, pellets, disks, fibers, gels, or particles such as cellulose beads, controlled pore-glass beads, silica gels, polystyrene beads optionally cross-linked with divinylbenzene and optionally grafted with polyethylene glycol and optionally functionalized with amino, hydroxy, carboxy, or halo groups, grafted co-poly beads, polyacrylamide beads, latex beads, dimethylacrylamide beads optionally cross-linked with N,N'-bis-acryloyl ethylene diamine, glass particles coated with hydrophobic polymer, etc., i.e., material having a rigid or semi-rigid surface; and

b) soluble supports such as low molecular weight non-cross-linked polystyrene.

It is intended that the definitions of any substituent or symbol (e.g., R^3) in a particular molecule be independent of its definitions elsewhere in the molecule. Thus, NR^3R^3 represents NH_2 , $NHCH_3$, $N(CH_3)_2$, etc.

Optical Isomers-Diastereomers-Geometric Isomers-Tautomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms which may be defined in terms of absolute stereochemistry as (R) or (S). The present invention is meant to comprehend all such possible

diastereomers as well as their racemic and optically pure forms and mixtures thereof. Optically active (R) and (S) forms may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. Likewise, all tautomeric forms are intended to be included.

Salts

The pharmaceutical compositions of the present invention comprise a compound of Formula II as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and, optionally, other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including organic and inorganic acids or bases.

When a compound of the present invention is acidic, salts may be prepared from pharmaceutically acceptable non-toxic bases. Salts derived from all stable forms of inorganic bases include aluminum, ammonium, calcium, copper, iron, lithium, magnesium, manganese, potassium, sodium, zinc, etc. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-

toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, isopropylamine, lysine, methylglucosamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purine, theobromine, triethylamine, trimethylamine, tripropylamine, etc.

When a compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, etc. Particularly preferred are citric, hydrobromic, maleic, phosphoric, sulfuric, and tartaric acids.

In the discussion of methods of treatment herein, reference to the compounds of Formula II is meant to also include the pharmaceutically acceptable salts thereof.

Utilities

The ability of the compounds of Formula II to interact with α adrenergic receptors indicates that the compounds are useful to treat, prevent, or ameliorate hypertension and benign prostate hypertrophy in mammals, especially in humans.

The ability of the compounds of Formula II to interact with dopamine receptors indicates that the compounds are useful to treat, prevent, or ameliorate Alzheimer's disease and depression in humans.

The ability of the compounds of Formula II to interact with θ -opiate receptors indicates that the compounds are useful to treat, prevent, or ameliorate schizophrenia in mammals, especially humans.

The ability of the compounds of Formula II to interact with K^+ channels indicates that the compounds are useful to treat, prevent, or ameliorate hypertension, asthma, and pulmonary insufficiency in mammals, especially humans.

The ability of certain compounds of Formula II to inhibit carbonic anhydrase isozymes makes them useful for preventing or reversing the symptoms induced by these enzymes in a mammal. This enzyme inhibition indicates that the compounds are useful to treat, prevent, or ameliorate ocular diseases, particularly glaucoma in mammals, especially in humans.

Dose Ranges

The magnitude of the prophylactic or therapeutic

dose of the compounds of Formula II will vary with the nature and severity of the condition to be treated and with the particular compound of Formula II and its route of administration. In general, the daily dose range for anti-enzymic use lies in the range of 20 to 0.001 mg/kg body weight of a mammal, preferably 10 to 0.01 mg/kg, and most preferably 1.0 to 0.1 mg/kg, in single or divided doses. In some cases, it may be necessary to use doses outside these ranges.

When a composition for intravenous administration is employed, a suitable daily dosage range is from about 10 to 0.0005 mg (preferably 5 to 0.01 mg) compound of Formula II per kg body weight.

When a composition for oral administration is employed, a suitable daily dosage range is from about 20 to 0.001 mg (preferably 10 to 0.01 mg) compound of Formula II per kg body weight.

When a composition for ophthalmic administration is employed, a suitable daily dosage range is from about 10-0.01% (preferably 5.0-0.5% compound of Formula II, typically prepared as a 2.0-0.1% by weight solution or suspension of a compound of Formula II in an acceptable ophthalmic formulation.

The compounds of Formula II may also be used in combination with other pharmaceutically active ingredients. For example, a typical ocular formulation may comprise the compound alone or in combination with a β -adrenergic blocking agent such as timolol maleate or a parasympathomimetic agent

such as pilocarpine. When used in combination, the two active ingredients are present in approximately equal parts.

Pharmaceutical Compositions

5 Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dosage of a compound of Formula II. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, etc. routes may be
10 employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula II, or a
15 pharmaceutically acceptable salt thereof, as an active ingredient, and may also contain a pharmaceutically acceptable carrier and, optionally, other therapeutically active ingredients.

The compositions include compositions suitable
20 for oral, rectal, topical (including transdermal devices, aerosols, creams, ointments, lotions, and dusting powders), parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal
25 administration; although the most suitable route in any given case will depend largely on the nature and severity of the condition being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and

prepared by any of the methods well known in the art of pharmacy.

A compound of Formula II may be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the nature of the preparation desired for administration, i.e., oral, parenteral, etc. In preparing oral dosage forms, any of the usual pharmaceutical media may be used, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (e.g., suspensions, elixirs, and solutions); or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, etc. in the case of oral solid preparations such as powders, capsules, and tablets. Solid oral preparations are preferred over liquid oral preparations. Because of their ease of administration, tablets and capsules are the preferred oral dosage unit form. If desired, capsules may be coated by standard aqueous or non-aqueous techniques.

In addition to the dosage forms described above, the compounds of Formula II may be administered by controlled release means and devices such as those described in U.S.P. Nos. 3,536,809; 3,598,123; 3,630,209; 3,845,770; 3,916,899; and 4,008,719, which

are incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be prepared as discrete units such as capsules, cachets, or tablets each containing a predetermined amount of the active ingredient in powder or granular form or as a solution or suspension in an aqueous or nonaqueous liquid or in an oil-in-water or water-in-oil emulsion. Such compositions may be prepared by any of the methods known in the art of pharmacy. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers, finely divided solid carriers, or both and then, if necessary, shaping the product into the desired form. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granule optionally mixed with a binder, lubricant, inert diluent, or surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Ophthalmic inserts are made from compression molded films which are prepared on a Carver Press by subjecting the powdered mixture of active ingredient and HPC to a compression force of 12,000 lb. (gauge) at 149°C for 1-4 min. The film is

cooled under pressure by having cold water circulate in the platen. The inserts are then individually cut from the film with a rod-shaped punch. Each insert is placed in a vial, which is then placed in humidity cabinet (88% relative humidity at 30°C) for 2-4 days. After removal from the cabinet, the vials are capped and then autoclaved at 121°C for 0.5 hr.

The following are representative pharmaceutical dosage forms of the compounds of Formula II:

10	<u>I.M. Injectable Suspension</u>	<u>mg/mL</u>
	Compound of Formula II	10
	Methylcellulose	5
	Tween 80	0.5
	Benzyl alcohol	9
15	Benzalkonium chloride	1
	Water for injection to a total volume of 1 mL	
	<u>Tablet</u>	<u>mg/tablet</u>
	Compound of Formula II	25
	Microcrystalline cellulose	415
20	Povidone	14
	Pregelatinized starch	43.5
	Magnesium stearate	<u>2.5</u>
		500
	<u>Capsule</u>	<u>mg/capsule</u>
25	Compound of Formula II	25
	Lactose powder	573.5
	Magnesium stearate	<u>1.5</u>

600

AerosolPer canister

	Compound of Formula II	24 mg
	Lecithin, NF liquid concentrate	1.2 mg
5	Trichlorofluoromethane, NF	4.025 gm
	Dichlorodifluoromethane, NF	12.15 gm

Ophthalmic Solutionmg/mL

	Compound of Formula II	1
	Monobasic sodium phosphate 2H ₂ O	9.38
10	Dibasic sodium phosphate 12H ₂ O	28.48
	Benzalkonium chloride	1
	Water for injection to a total volume of 1 mL	

Ophthalmic Suspensionmg/g

	Compound of Formula II	1
15	Petrolatum liquid to a total weight of 1 g	

Ophthalmic Insertmg/insert

	Compound of Formula II	1
	Hydroxypropylcellulose	12

20 These compounds of Formulae I and II may also be
 used as libraries for discovering a new lead
 structures by evaluation across an array of
 biological assays, including the discovery of
 selective inhibition patterns across isozymes. These
 libraries are thus tools for drug discovery; i.e., as
 25 a means to discover novel lead compounds by screening

the libraries against a variety of biological targets and to develop structure-activity relationships in large families of related compounds. The libraries may be tested with the ligands attached to the solid supports as depicted in Formula I or the individual compounds II may be detached prior to evaluation. With the compounds of Formula I, screening assays such as FACS sorting, bead lawn assays, and cell lawn assays may be used. When a compound is detached prior to evaluation, its relationship to its solid support is maintained, for example, by location within the grid of a standard 96-well plate or by location of activity on a lawn of cells. The solid support associated with bioactivity or the solid support related to the detached ligand may then be decoded to reveal the structural or synthetic history of the active compound (Ohlmeyer *et al.*, *Proc.Natl.Acad.Sci. USA*, 90, 10922-10926, Dec. 1993).

Assays for Determining Biological Activity

The compounds of the present invention may be tested by assays well known in the art for interaction with α adrenergic receptors, interaction with dopamine receptors, interaction with θ -opiate receptors, interaction with K^+ channels, and carbonic anhydrase inhibition. For example, representative references teaching carbonic anhydrase inhibition assays are:

Carbonic Anhydrase Inhibition - Maren and Couto, "The Nature of Anion Inhibition of Human Red Cell Carbonic Anhydrases", *Archive. of Biochem. and Biophy.*, 196, No.2, Sept., 501-510 (1979).

5 Carbonic Anhydrase Inhibition - Ponticello et al., "Thienothiopyran-2-sulfonamides: A Novel Class of Water-Soluble Carbonic Anhydrase Inhibitors", *J. Med. Chem.*, 30, 591-597 (1987).

10 Carbonic Anhydrase Inhibition - It has now been found that the use of very low initial concentrations (0.04-1.6, preferably about 0.6, μM) of dansylamide and (0.03-1.2, preferably about 0.3, μM) of carbonic anhydrase to assay test compounds for carbonic anhydrase inhibition not only allows the use of very
15 small total volumes (approx. 25-100, preferably about, 50 μL) per assay but also allows one to distinguish high-affinity from low-affinity compounds without either re-elution or re-synthesis of the test compound. By increasing the concentration of
20 dansylamide from $\sim 0.1 \mu\text{M}$ to $\sim 200 \mu\text{M}$ directly in the assay sample, relatively weak inhibitors can be distinguished from relatively strong inhibitors on the same aliquot of test compound. The small total volume advantageously permits high throughput
25 assaying of small quantities of test compounds, for example, in 96-well plates, and the reduced concentration of dansylamide advantageously permits the detection of test compounds that have a wide

range (≤ 500 nm) of characteristic dissociation constants. The following materials are used:

	100.	mM sodium phosphate buffer, pH 7.4
	0.6	μ M dansylamide (Sigma D-3882)
5	0.3	μ M bovine carbonic anhydrase inhibitor (Sigma C-3934)

Reactions are carried out in 50 μ L total volume in 96-well plates, preferably, Dynatech MicroFluor plates, white with 'U' bottom, containing the test compounds. The assay mix is prepared immediately before use, and 50 μ L of the assay solution is pipetted into each well of plates in which the test compounds are previously dried. The plates are spun briefly in a tabletop centrifuge before reading fluorescence. Fluorescence is read in a Perkin-Elmer LS 50B spectrofluorimeter fitted with a Well Plate Reader Accessory using an excitation wavelength of 274 nm (2.5 nm slit) and an emission wavelength of 454 nm (20 nm slit), with a 390 nm cutoff filter in place. Fluorescence measurements are averaged over 1 sec for each well. To identify wells in which inhibitors are present, first a plate with no exogenous inhibitors is read, which typically gives a fluorescence reading of 2.6-3.1 (typical standard deviation ± 0.06) for a given assay solution. In plates containing inhibitor candidates, active inhibitors cause a decrease in the fluorescence signal of greater than 5 times the standard deviation.

To distinguish high-affinity from low affinity candidates, 5 μ L of a 2 mM stock of dansylamide in DMSO is added to the above test solution, and the assay repeated as above. Typical readings are 7.5 to 8.5 \pm 0.4 (standard deviation) among previously identified inhibitors. High-affinity compounds lower the signal by greater than 3 standard deviations). Thus, the increased concentration of dansylamide is sufficient to displace relatively weak inhibitors (e.g., chlorothiazide, K_i ~75 nM) without displacing relatively strong inhibitors (e.g., acetazolamide, k_i ~7.5 nM).

Bead Lawn Assay (General Method). An enzyme of interest is incorporated into a gellable gum such as silica gel, agar, agarose, pectin, polyacrylamide, gelatin, starch, and gellan gum, preferably a low melting-temperature agarose gel (0.5-2.0%, wt./vol.), which is layered on top of a lawn, no greater than one bead in thickness, of solid supports with attached ligands. The detection of an active combinatorial library member is accomplished by photoeluting the ligands from the beads *in situ* by exposure to U.V. light. To minimize premature photoelution, the beads are preferably protected from ambient light sources prior to U.V. exposure. The beads are evaluated by placing a second layer, preferably low-melt agarose gel, containing a substrate on top of the one containing the enzyme and the photoreleased library members, and allowing

enzymic conversion of substrate into product by diffusion of the substrate into the enzyme-containing gel. The substrate is preferably one that produces a photometric change upon conversion into product; e.g., the generation of a colored product, a fluorescent product, or a chemiluminescent reaction (where one of the products is a photon). The second layer may comprise a gellable gum such as silica gel, agar, agarose, pectin, polyacrylamide, gelatin, starch, and gelatin gum, or a solid material such as a matrix containing an array of fluorogenic-pellets. Inhibition of the enzyme by a library member results in a difference in appearance in the vicinity of the attached bead and allows for selection of the bead and the identifiers which encode for the inhibitor. This technique may be used with a variety of enzymes, for example:

Acid Phosphatase	Furin
Activated Protein C	γ -
	Glutamyltranspeptidase
Alkaline Phosphatase	Granzymes A & B
Aminopeptidases B & M	HIV Protease
Amyloid A4-Generating Enzyme	IL-1B Convertase
Angiotensinase	Kallikrein
Aryl Sulfatase	Lysozyme
β -Galactosidase	Mast Cell Protease
β -Glucosidase	Peroxidase
β -Glucuronidase	Plasmin
Calpains I & II	Prohormone Convertase

5	Cathepsins B, C, D, & G	rANP Precursor
		Processing Enzyme
	Cholinesterase	Renin
	Chymotrypsin	Spleen Fibrinolytic
		Proteinase
	Collagenase	Staphylocoagulase
	Dipeptidyl Peptidases I-IV	Thrombin
10	Elastase	Tissue Plasminogen
		Activator
	Endothelin Converting Enzyme	Trypsin
	Factor Xa	Tryptase
	Factor XIa	Urokinase
	Factor XIIa Df-Protease	

15 A bead lawn assay for testing carbonic anhydrase inhibition preferably comprises agarose for both layers, bovine carbonic anhydrase, and fluorescein diacetate.

20 Bead Lawn Assay (Carbonic Anhydrase). Beads to be tested are arrayed in a minimal amount of methanol in a 60 mm polystyrene tissue culture dish and then all the methanol allowed to evaporate. A 2.5% (wt./vol.) mixture of agarose (SeaPlaque, FMC BioProducts, Rockland, ME) in 20 mM sodium phosphate buffer (pH 7.4) is heated on a hot plate until the

25 agarose dissolves and then is equilibrated to 37°C in a water bath. A separate stock of the same buffer is also equilibrated to 37°C. The enzyme layer is prepared as follows: 100 µL of a bovine carbonic

anhydrase stock (0.5 mg/mL or 53 μ M based on absorbance at 280 nm, Sigma #C-3934) is added to 2.15 mL of buffer, and 1.25 mL agarose solution is added to the mixture. The agarose/enzyme solution is poured onto the dish containing the beads and the agarose is allowed to solidify at r.t. for 3-5 min. To identify zones of inhibitions, the compounds, which are optionally photoeluted by exposure to 4.7-6 mW/Cm² 365 nm UV light for 5 sec. to 1 hr., are overlaid with fluorescein diacetate (FLDA, Molecular Probes, Eugene, OR), which is prepared as follows: to 2.25 mL phosphate buffer is added 10 μ L FLDA stock (10 mM in DMF at -20°C) and 1.25 mL agarose (final FLDA concentrations: 30 μ M). The solution is mixed thoroughly then poured over the enzyme layer in the dish. Zones of inhibition appear after 1-2 min. and intensify over 30-45 min. They are dark against a yellow-green background when illuminated by short-wave UV light (λ_{max} =254 nm).

Bead Lawn Assay (Inositol Monophosphatase). The assay is similar to that for carbonic anhydrase, with the following substitutions: The buffer used is 20 mM Tris, 1 mM EGTA, pH 7.8. The enzyme layer contains 1 mg/mL recombinant human inositol monophosphatase (purified from *E. coli*) and 10 mM MgCl₂. Three alternative substrates are used: methylumbelliferyl phosphate (Sigma, M-8883), a fluorogenic substrate, detected using filters around λ_{ex} =388 nm and λ_{em} =420 nm; or CSPD or CDP-Star (chemiluminescent substrates

for alkaline phosphatase, Tropix, Bedford MA), detected directly without requiring filters. The preferred substrate is CSPD.

Methods of Synthesis

5 The compounds of the present invention can be prepared according to the following methods. At each step in the synthesis each solid support upon which a compound is being synthesized is uniquely tagged to define the particular chemical event(s) occurring during that step. The tagging is accomplished using identifiers such as those of Formula IV, which record the sequential events to which the support is exposed during the synthesis, thus providing a reaction history for the compound produced on each support.

10 The identifiers are used in combination with one another to form a binary or higher order encoding scheme permitting a relatively small number of identifiers to encode a relatively large number of reaction products. For example, when used in a binary code, N identifiers can encode up to 2^N different compounds and/or conditions. By associating each variable or combination of variables at each step of the synthesis with a combination of identifiers which uniquely define the chosen variables such as reactant, reagent, reaction conditions, or combinations of these, one can use the identifiers to define the reaction history of each solid support.

15

20

25

In carrying out the syntheses, one begins with at least 10^3 , desirably at least 10^4 , and generally not exceeding 10^{15} solid supports. Depending on the pre-determined number of R^1/R^2 choices for the first step, one divides the supports accordingly into as many containers. The appropriate reagents and reaction conditions are applied to each container and the combination of identifiers which encode for each R^1/R^2 choice is added and attached. Depending on the chemistries involved, the tagging may be done prior to, concomitantly with, or after the reactions which comprise each choice. As a control, sample supports may be picked at any stage and a portion of their tags detached and decoded to verify that the correct tags are bound to the sample supports. As needed, one may wash the beads free of any excess reagents or by-products before proceeding. At the end of each step, the supports are usually combined, mixed, and again divided, this time into as many containers as pre determined for the number of choices for the second step in the synthesis. This procedure of dividing, reacting, tagging, and remixing is repeated until the combinatorial synthesis is completed.

Scheme 1

Functionalized supports such as amino-functionalized or hydroxy-terminating PEG grafted polystyrene beads are divided into a pre-determined number of reaction vessels and are reacted with a cleavable linker/ligand element 3, which has been

pre-formed, to generate 4. Unique tagging of the supports in each reaction vessel is achieved with combinations of identifiers encoded in a binary scheme, e.g., as depicted in Table 1-1 for three choices of R^1 and R^2 . The identifiers are attached by adding a solution of the identifiers (in a 1.5% wt./wt. identifier:solid support ratio) to a batch of supports suspended in CH_2Cl_2 , and shaking the mixture for 30 min. A dilute solution of rhodium trifluoroacetate dimer is added and the mixture is immediately shaken 4 hr and washed in CH_2Cl_2 . The procedure is repeated and the mixture shaken for 14 hr and then washed in DMF/DCM.

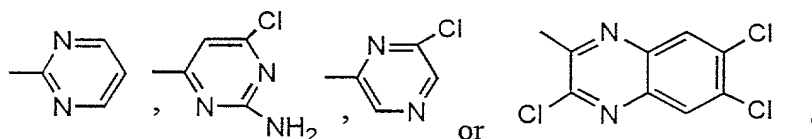
Scheme 2

The compounds 4 are pooled, mixed, and divided into a pre-determined number of reaction vessels, each of which is treated with one reagent corresponding to ligand element $=CR^4R^5$, in the presence of pyrrolidine to produce 5a, 5b, and 5c. Unique tagging of the supports in each reaction vessel is achieved with combinations of additional identifiers encoded in a binary scheme, e.g., as depicted in Table 1-2 for seven choices of R^4R^5 .

Scheme 3

The compounds 5c, where $R^4/R^5/X$ represents the residue of piperidine, pyrrolidine, or aminocyclohexane, are pooled, mixed, and then divided into a pre-determined number of reaction vessels.

The supports in each reaction vessel are uniquely tagged with combinations of additional identifiers encoded in a binary scheme, e.g., as depicted in Table 1-3 for 30 choices of R^8 and in Table 1-5 for six choices of R^{14} and four choices of heteroaryl groups. After removal of any N-protecting Boc group in R^4R^5 , each reaction vessel is treated with one reagent corresponding to ligand element R^8 in the presence of solvents such as CH_2Cl_2 , DMF, or EtOH and, when required, bases such as triethylamine or 2,6-lutidine to produce 6 having an R^8 substituent at C-2 and a ketone at C-4, i.e., when R^6R^7 together are 0. In scheme 3, R^{14} is benzyl, $-CH_2-Ph-4-F$, $CH_2-Ph-4-OCH_3$, $-CH_2-4-Py$, n-pentyl, or $-CH_2-c-propyl$; and heteroaryl is



Scheme 4

A portion of the compounds 5a, 5b, 5c, and 6 may be pooled, mixed, and then divided into a pre-determined number of reaction vessels where they may be uniquely tagged with combinations of additional identifiers encoded in a binary scheme, e.g., as in Table 1-4 for three choices of R^6/R^7 . Each vessel is treated with sodium borohydride to yield 7 as an alcohol at C-4 or is treated with 1,2-dithioethane and a Lewis acid such as $BF_3 \cdot Et_2O$ to yield 8 as a dithiolane at C-4, or is treated with an appropriate

non-beta branched primary amine in the presence of NaCNBH₃ in MeOH, optionally with acetic acid, to yield secondary amine 9, or is left untreated.

5 Compounds 5a, 5b, 5c, 5d, 6, 7, 8, and 9 are then exposed to UV light (~360 nm) in polar solvents such as DMSO, H₂O, or a lower alkanol such as MeOH to cleave the compounds of Formula II from the support/linker complex.

Scheme 5

10 TentaGel resin may be modified with bis-Boc Lysine to increase the available reaction sites for ligand attachment Bis-Boc-lysine in DMF, HOBt, and DIC are shaken at r.t. and then dry TentaGel resin is added. The mixture is shaken at r.t. for 17 hr and
15 then washed alternately with methanol and DCM and then with THF and dried under vacuum. To deprotect the resin, DCM is added, followed by a 30% TFA solution in DCM (100mL). The vessel is shaken at room temperature for 15 min. before adding neat TFA.
20 The vessel is shaken at room temperature for 2.5 hr at which time the resin is washed with DCM, then treated with a solution of 10% triethylamine in DCM, then washed with DCM and DMF.

25 For purposes of simplicity, the schemes do not show the use of this bis modification.

Scheme 6

Functionalized supports such as amino-functionalized or hydroxy-terminating PEG grafted polystyrene beads are divided into a pre-determined number of reaction vessels and are reacted with a cleavable linker/ligand element 10, which has been pre-formed, to generate 11. Unique tagging of the supports in each reaction vessel is achieved with combinations of identifiers encoded in a binary scheme, e.g., as depicted in Table 2-1 for seven choices of $-(CH_2)_{1-6}R^{17}$. The identifiers are attached by adding a solution of the identifiers (in a 7% wt./wt. identifier:solid support ratio) to each batch of supports suspended in EtOAc and shaking the mixture for 1 hr. A dilute solution of rhodium trifluoroacetate dimer in DCM is added and the mixture is shaken 15 hr and washed with DCM (4X) and EtOAc (2X). The procedure is repeated for each identifier.

To deprotect the encoded resin, it is suspended in DCM and then agitated with a TFA solution in DCM. The resin is then washed with DCM followed by treatment with triethylamine in DCM and then washed with DCM.

Scheme 7

The compounds 12 are pooled, mixed, and divided into a pre-determined number of reaction vessels, each of which is treated with one acetophenone

reagent corresponding to ligand element R^2 , in the presence of DIC, HOBT, and DMF to produce 4'. Unique tagging of the supports in each reaction vessel is achieved with combinations of additional identifiers encoded in a binary scheme analogous to that in Table 2-1.

Scheme 8

The compounds 4' are mixed, pooled, and divided into a predetermined number of reaction vessels, each of which is treated with an aldehyde or ketone element corresponding to R^4/R^5 in the presence of pyrrolidine in methanol at 75°C to produce the compounds 5a', 5b', and 5c'. Unique tagging of the supports in each reaction vessel is achieved with combinations of additional identifiers encoded in a binary scheme analogous to that in Table 2-1.

Scheme 9

The compounds 5c', where $R^4/R^5/X$ represents the residue of t-Boc protected piperidine, t-Boc protected aminocyclohexane, or other amine functionalized molecules are mixed, pooled, and divided into a predetermined number of reaction vessels. The supports in each reaction vessel are uniquely tagged with combinations of additional identifiers encoded in a binary scheme analogous to that in Table 2-1. After removal of any N-protecting group in R^4/R^5 , each vessel is treated with one reagent such as a chloroformate, isocyanate,

thioisocyanate, carboxylic acid, alkyl or aryl sulfonyl halide, aldehyde, or a haloheteroaromatic compound corresponding to ligand element R⁸ in the presence of solvents such as CH₂Cl₂, DMF, EtOH, or methanol. When required, bases such as triethylamine, DBU, or 2,6-lutidine and/or other reagents or combinations of reagents such as DIC, NaCNBH₃, HOBT, and acetic acid are added to produce 6', having an R⁸ substituent at C-2 and a ketone at C-4, i.e. when R⁶R⁷ together are O.

Scheme 10

A portion of compounds 5a', 5b', 5c', and 6' may be pooled, mixed, and then divided into a predetermined number of reaction vessels where they may be uniquely tagged with combinations of additional identifiers encoded in a binary scheme analogous to that in Table 2-1. Each vessel is treated with 1) sodium borohydride in methanol to yield 7' as an alcohol at C-4; 2) 1,2-dithioethane and a Lewis acid such as boron trifluoride etherate to yield 8' as the dithiolane at C-4; 3) an unhindered primary amine along with NaCNBH₃ in acetic acid/methanol solvent at ca. 75°C to yield 9' as an amine at C-4; or 4) is left untreated.

Scheme 11

The compounds 9 or 9' are divided into a predetermined number of reaction vessels. Each vessel is treated with one reagent such as a

chloroformate, isocyanate, thioisocyanate, carboxylic acid, alkyl or aryl sulfonyl halide, aldehyde, or a haloheteroaromatic compound corresponding to ligand element R¹⁵ in the presence of solvents such as CH₂Cl₂, DMF, EtOH, or methanol. When required, bases such as triethylamine, DBU, or 2,6-lutidine and/or other reagents or combinations of reagents such as DIC, NaCNBH₃, HOBT, and acetic acid are added to produce the corresponding compound 13 or 13'.

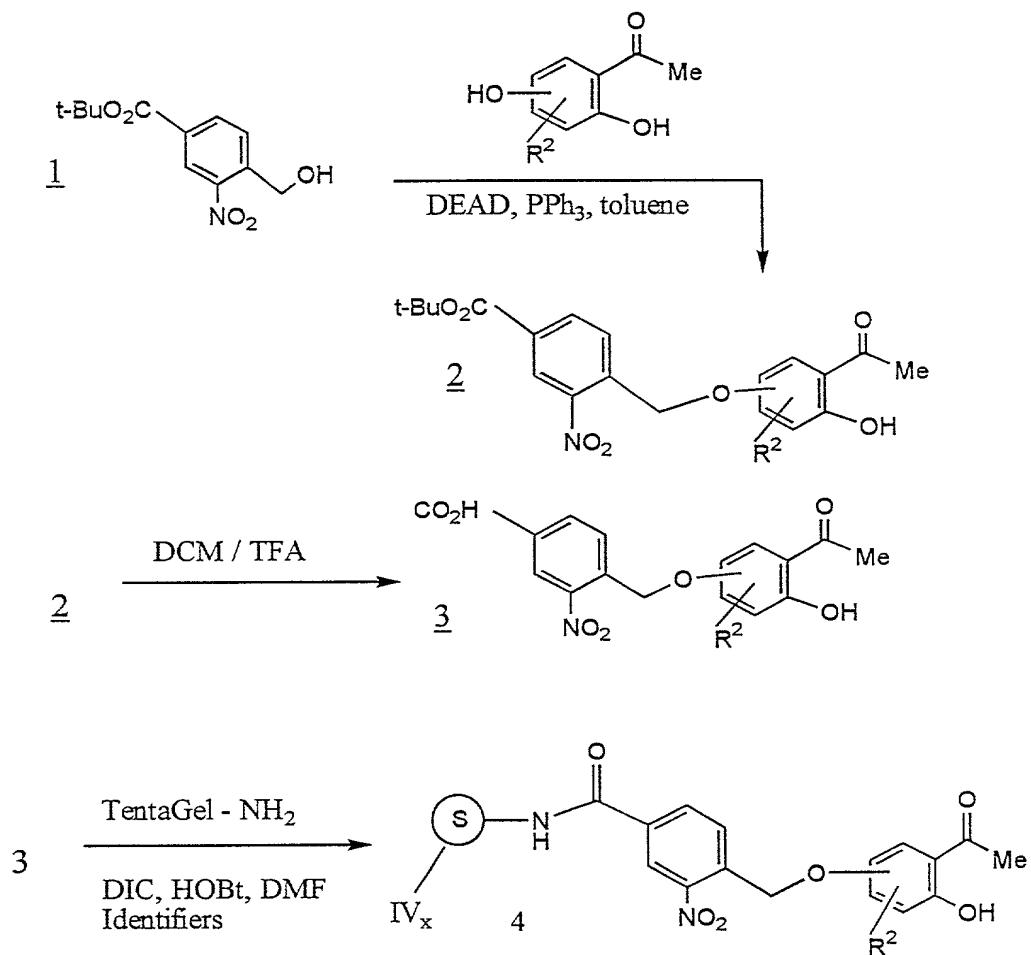
Scheme 12

Functionalized supports such as amino-functionalized or hydroxy-terminating PEG grafted polystyrene beads are placed into a reaction vessel and are reacted with a cleavable linker/ligand element 10, which has been pre-formed, to generate 11'. To deprotect the resin, it is suspended in DCM and then agitated with TFA solution in DCM. The resin is then washed with DCM followed by treatment with triethylamine in DCM and then washed with DCM to yield 12'.

In an appropriately sized synthesis vessel is placed HOBT (3 equiv.) and the carboxylic acid Q(X=OH) (3 equiv.) in a solvent such as DMF. DIC (3 equiv.) is added and the vessel agitated for 15 min. before adding the amino resin 12' (1 equiv. of amino sites). The resin is agitated for 5 hrs., then washed with alternating DCM and MeOH (5X each) and then with THF (2X) to yield 14.

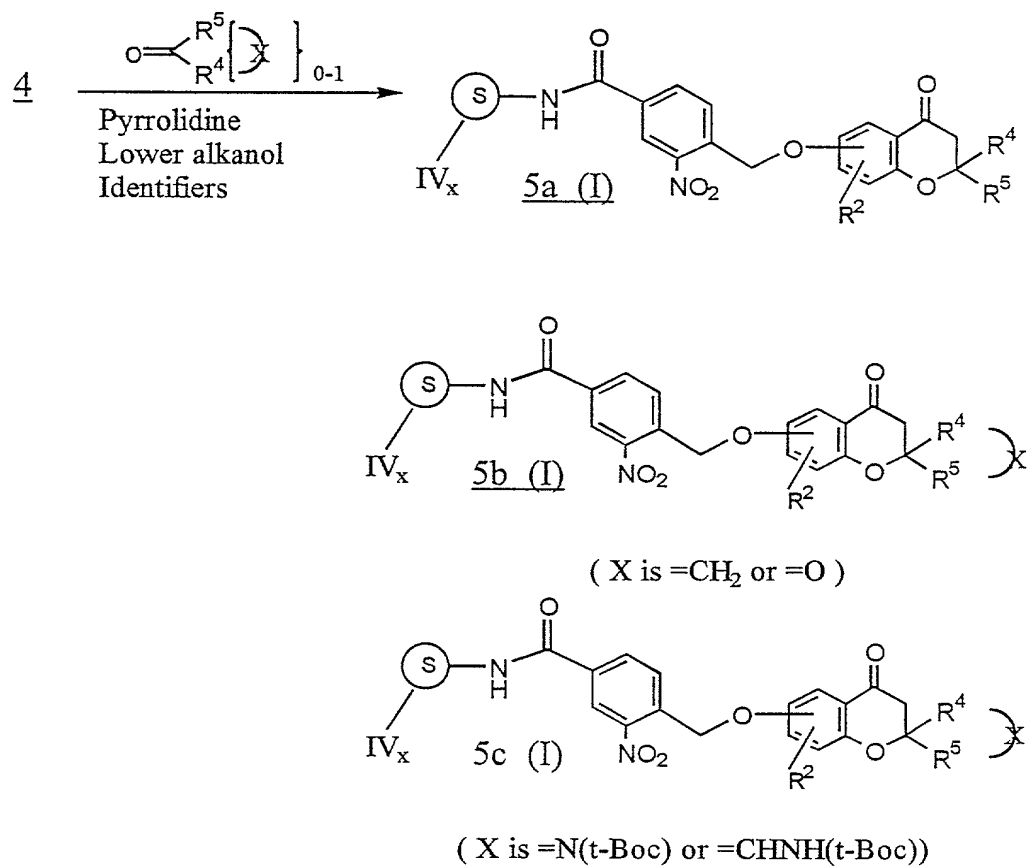
In an appropriately sized synthesis vessel is placed the amino resin 12' (1 equiv. of amino sites). A solvent such as DCM is added, followed by an organic base such as triethylamine, pyridine, Hunig's base (di-isopropylethylamine), or 2,6-lutidine (10 equiv.). The resin is agitated for 15 min. before adding the acid halide Q (X=Cl, Br) (5 equiv.) as a dilute solution in a solvent such as DCM. The resin is agitated for 4 hrs. and then washed with DCM and MeOH (5X each) to yield 14.

SCHEME 1
LINKER / 1st LIGAND ELEMENT

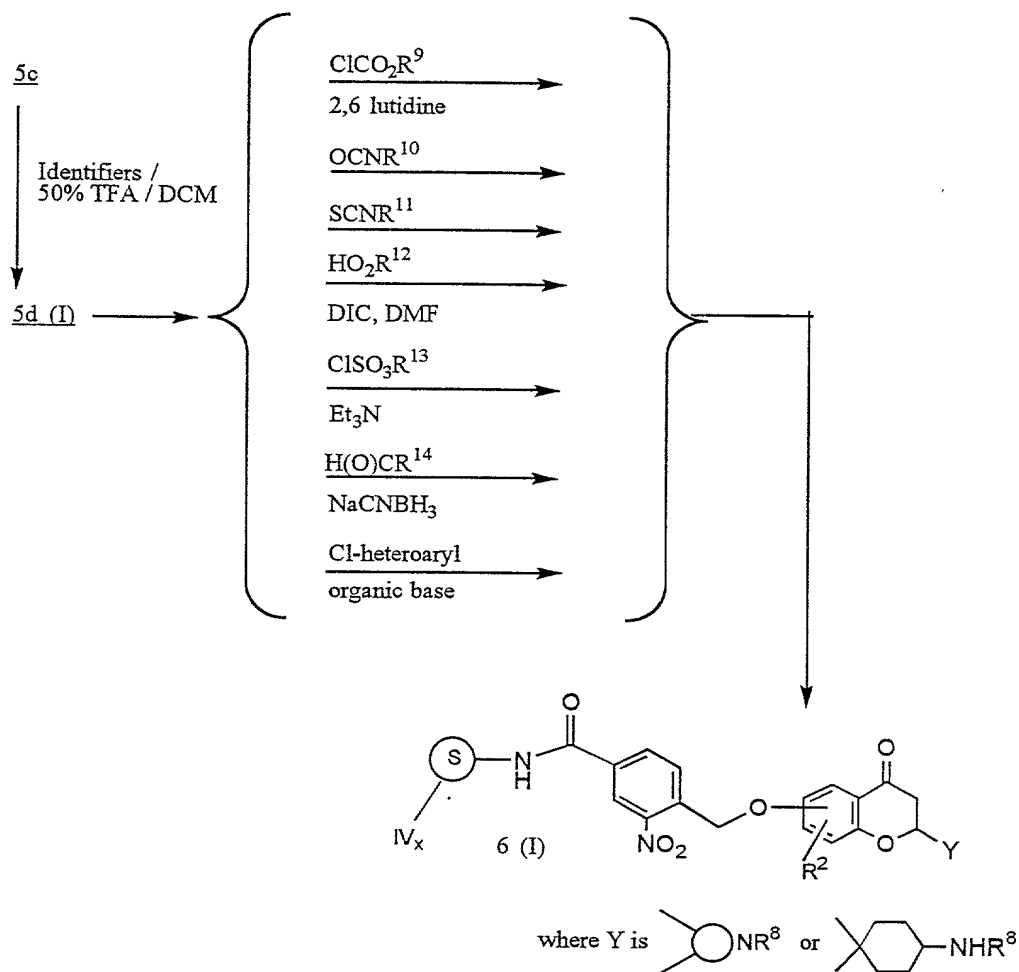


x is 1-30, depending on the binary code for the selected solid support

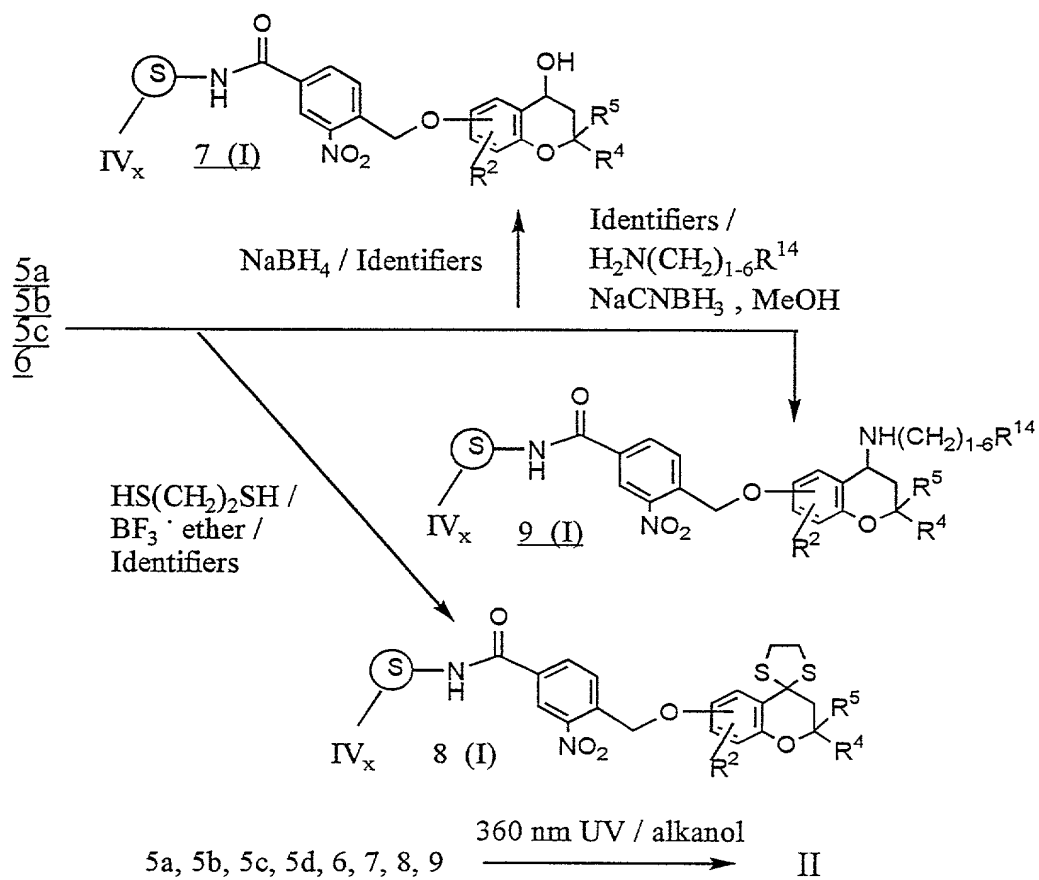
SCHEME 2
ADDITION OF R⁴ / R⁵

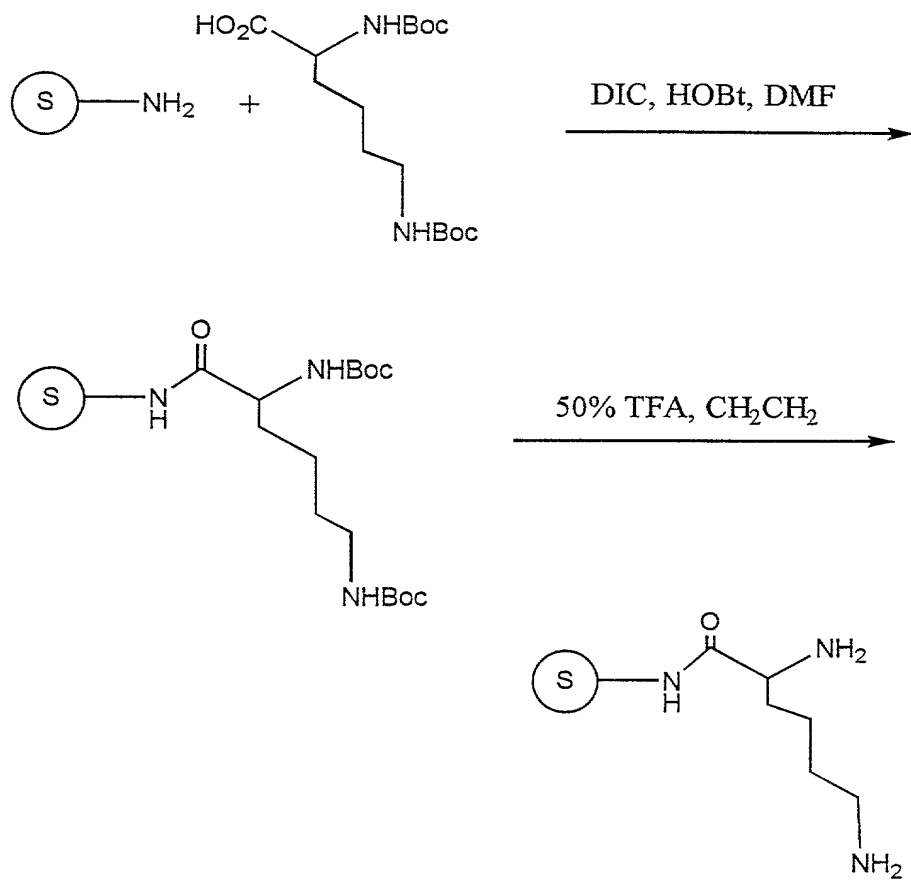


SCHEME 3
ADDITION OF R⁸

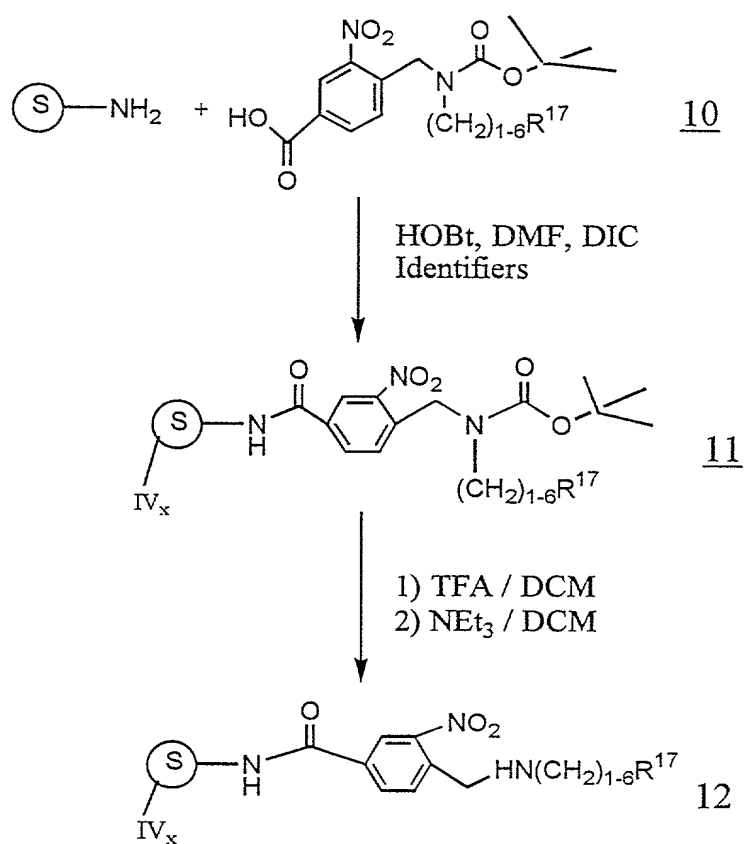


SCHEME 4
ADDITION OF R⁶ / R⁷

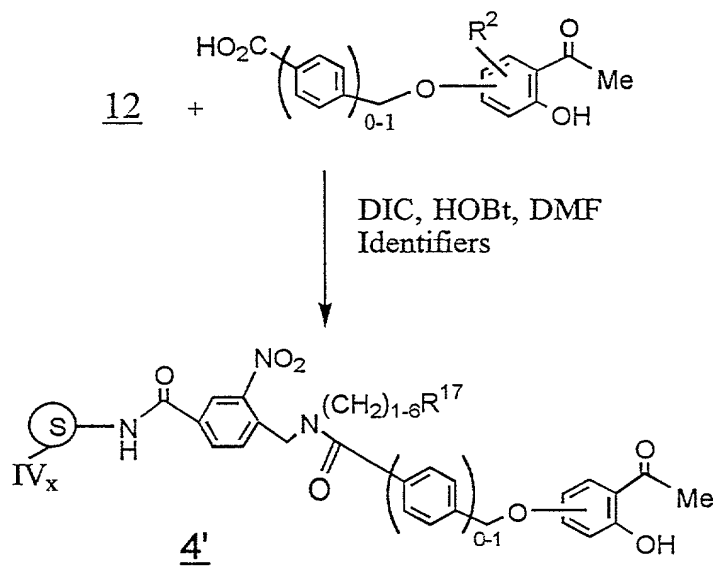


SCHEME 5
BIS-LINKER ATTACHMENT

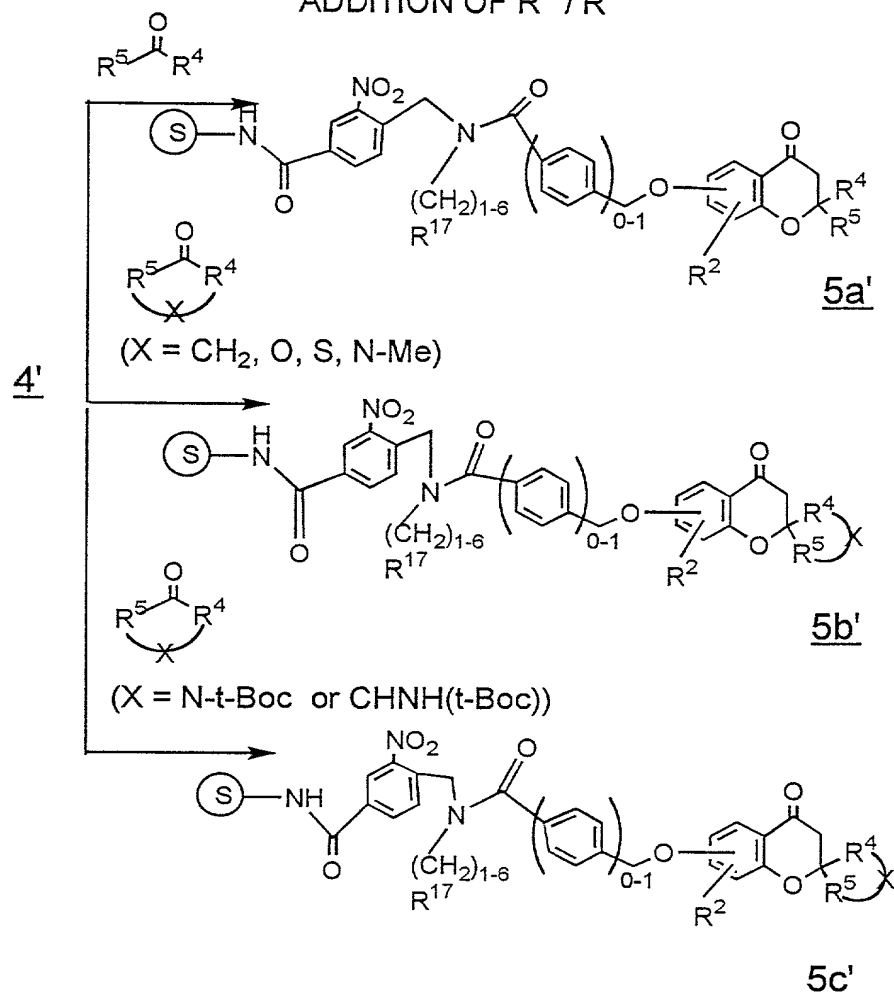
SCHEME 6
CLEAVABLE LINKER / 1st LIGAND ELEMENT



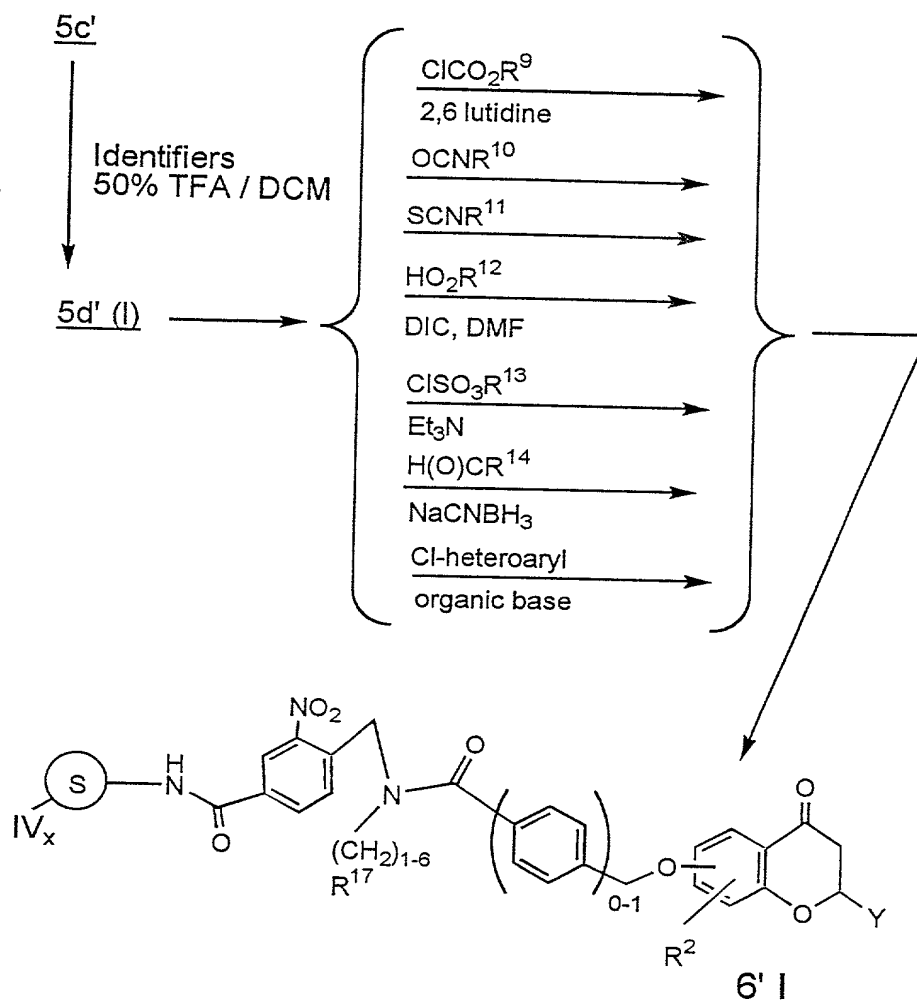
SCHEME 7
ATTACHMENT OF HYDROXYACETOPHENONES


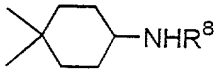
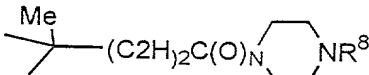


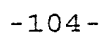
SCHEME 8
ADDITION OF R⁴ / R⁵



SCHEME 9
ADDITION OF R⁸



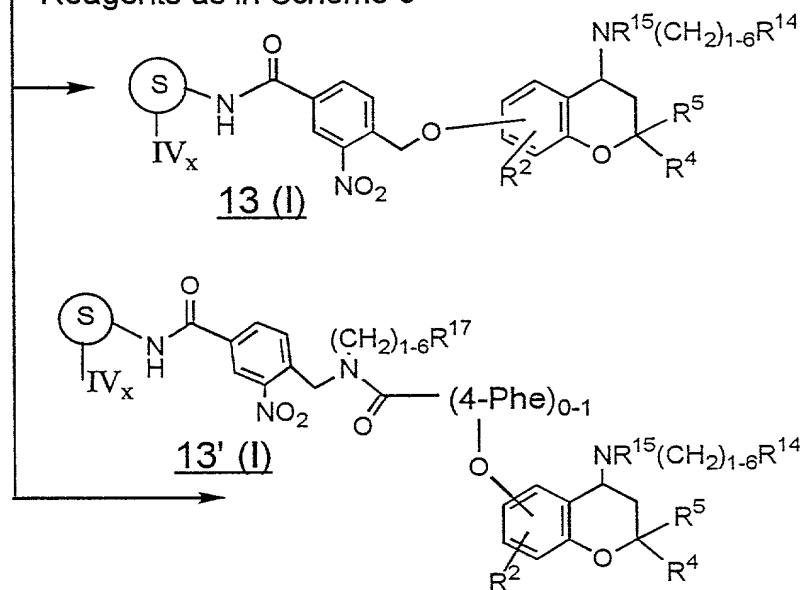
where Y is , , or 



SCHEME 11
ADDITION OF R¹⁵

9, 9'

Reagents as in Scheme 9



SCHEME 12
COMBINATORIAL SYNTHONS

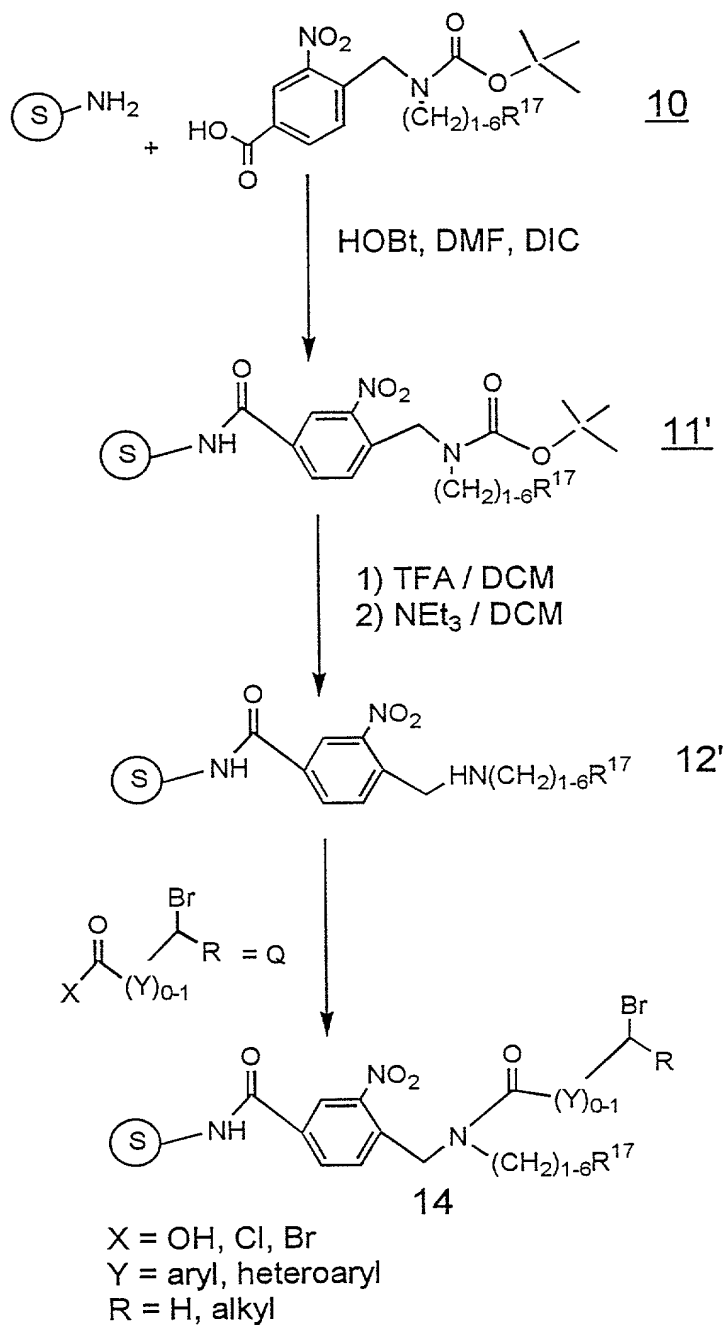


Table 2 illustrates compounds of Formula II which are representative of the present invention:

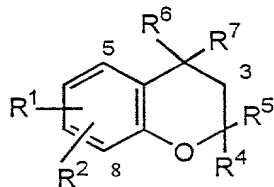


TABLE 2
REPRESENTATIVE COMPOUNDS

R ¹	R ²	R ⁴	R ⁵	R ⁶	R ⁷
6-OH	8-CH ₃	C ₂ H ₅	C ₂ H ₅	OH	H
7-OH	8-CH ₃	CH ₃	CH ₃	H	OH
5-OH	7-C ₂ H ₅	H	CH ₂ H ₅	NH ₂	H
6-OH-(CH ₂) ₂ OH	H	C ₃ H ₇	CH ₃	=O	
7-OCH ₂ CO ₂ H	7-CH ₂ H ₅	-(CH ₂) ₄ -	H	morpholino	
8-O-(CH ₂) ₂ OH	H	-(CH ₂) ₅ -	N(CH ₃) ₂	H	
6-CO ₂ H	8-CH ₃	-(CH ₂) ₆ -	-S(CH ₂) ₂ S-		
6-OH	H	-(CH ₂) ₂ O(CH ₂) ₂ -	=O		
7-OH	8-CH ₃	CH ₃	CH ₃	-S(CH ₂) ₂ S-	
6-OH	H	-(CH ₂) ₅ -	=O		

Table 3 illustrates additional compounds of Formula II representative of the present invention:

TABLE 3
REPRESENTATIVE COMPOUNDS

5

R ¹	R ²	R ⁴ /R ⁵	R ⁶	R ⁷	R ⁸
6-OH	H	-(CH ₂) ₂ NR ⁸ (CH ₂) ₂ -	OH	H	-CONH-Ph-4-CF ₃
7-OH	8-CH ₃	-CH ₂ NR ⁸ (CH ₂) ₃ -	-N \square SO ₂	H	-SO ₂ -2-Naph
5-O(CH ₂) ₂ OH	7-C ₂ H ₅	-(CH ₂) ₂ NR ⁸ CH ₂ -	-N \square	H	-CSNH-Ph
6-OH	H	-(CH ₂) ₂ NR ⁸ (CH ₂) ₂ -	=O		-CO-Ph-4-SO ₂ NH ₂
7-OH	H	-(CH ₂) ₂ CH(NR ⁸)(CH ₂) ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
6-OH	H	-(CH ₂) ₂ NR ⁸ (CH ₂) ₂ -	=O		-COCH ₂ Ph
6-OH	H	-(CH ₂) ₂ NR ⁸ CH ₂ -	-S(CH ₂) ₂ S-		-CO ₂ -2-Py
7-OH	8-CH ₃	-(CH ₂) ₂ NR ⁸ (CH ₂) ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
6-OH	H	-(CH ₂) ₂ NR ⁸ CH ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂

Table 3 (Con't.)

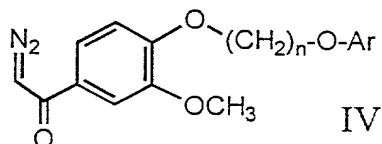
7-OH	H	$-(\text{CH}_2)_2\text{NR}^8-$ $(\text{CH}_2)_2-$	=O		-CO-Ph-4-SO ₂ NH ₂
6-OH	H	$-(\text{CH}_2)_2\text{NR}^8-$ $(\text{CH}_2)_2-$	OH	H	CONH-Ph-4-CF ₃
7-OH	8-CH ₃	$-(\text{CH}_2)_2\text{NR}^8-$ CH ₂ -	N(CH ₃) ₂	H	-SO ₂ -2-Naph
5-O(CH ₂) ₂ OH	7-C ₂ H ₅	$-(\text{CH}_2)_2\text{NR}^8-$ CH ₂ -	-SCH ₂ CH- (CH ₃)S-	H	-CSNH-Ph
6-OH	H	$-(\text{CH}_2)_2\text{NR}^8-$ $(\text{CH}_2)_2-$	=O		-CO-Ph-4-SO ₂ NH ₂
7-OH	H	$-(\text{CH}_2)_2\text{NR}^8-$ $(\text{CH}_2)_2-$	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
6-OH	H	$-(\text{CH}_2)_2\text{NR}^8-$ $(\text{CH}_2)_2-$	=O		COCH ₂ Ph
6-OH	H	$-(\text{CH}_2)_2\text{NR}^8-$ CH ₂ -	-S(CH ₂) ₂ S-		-CO ₂ -2-Py
7-OH	8-CH ₃	$-(\text{CH}_2)_2\text{NR}^8-$ $(\text{CH}_2)_2-$	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
6-OH	H	$-(\text{CH}_2)_2\text{NR}^8-$ CH ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
7-OH	H	$-(\text{CH}_2)_2\text{NR}^8-$ $(\text{CH}_2)_2-$	=O		-CO-Ph-4-SO ₂ NH ₂

The invention is further defined by reference to the following examples, which are intended to be
 5 illustrative and not limiting.

PREPARATION 1

IDENTIFIERS

Twelve compounds of the general formula:



10 wherein:

n=3-12 and Ar is pentachlorophenyl or
n=5-6 and Ar is 2,4,6-trichlorophenyl
were prepared according to Scheme 13 and the
following illustrative example.

- 5 a) Methyl vanillate (0.729 g, 4.0 mmol), 1-
hydroxy-9-(2,3,4,5,6-pentachlorophenoxy)nonane
(1.634g, 4.0 mmol) and triphenylphosphine (1,258 g,
4.8 mmol) were dissolved in 20 mL dry toluene under
argon. DEAD (0.76 mL, 0.836 g, 4.8 mmol) was added
10 dropwise and the mixture was stirred at 25°C for one
hr. The solution was concentrated to half volume and
purified by flash chromatography eluting with DCM to
give 1.0 g (1.7 mmol, 43%) of the product as a white
crystalline solid.
- 15 b) The methyl ester from Step (a) (1.0 g, 1.7
mmol) was dissolved in 50 mL THF, 2 mL water was
added, followed by LiOH (1.2 g, 50 mmol). The
mixture was stirred at 25°C for one hr. then refluxed
for 5 hr. After cooling to 25°C, the mixture was
20 poured onto ethyl acetate (200 mL) and the solution
was washed with 1 M HCl (3x 50 mL) then sat'd aq.
NaCl (1x 50mL) and dried over sodium sulfate. The
solvent was removed and the crude acid azeotrope
once with toluene. The crude material was dissolved
25 in 100 mL toluene, 10 mL (1.63 g, 14 mmol) thionyl
chloride was added, and the mixture was refluxed for
90 min. The volume of the solution was reduced to
approx. 30 mL by distillation, then the remaining
toluene was removed by evaporation.

c) The crude cid chloride from Step (b) was dissolved in 20 mL dry DCM and cooled to -70°C under argon and a solution of approx. 10 mmol diazomethane in 50 mL anhydrous ether was added. The mixture was warmed to r.t. and stirred for 90 min. Argon was bubbled through the solution for 10 min., then the solvents were removed by evaporation and the crude material was purified by flash chromatography, eluting with 10-20% ethyl acetate in hexane. The diazoketone (0.85 g, 1.4 mmol, 82% yield over three steps) was obtained as a pale yellow solid.

In alternate Step (c) there is a change to the final diazomethylation step, whereby the acid chloride is reacted with (trimethylsilyl)diazomethane and triethylamine to give the identifier, which can then be used without further purification. With this alternate step, the identifier can be obtained in high yield with no chloromethylketone byproduct. Also, purification by flash chromatography is no longer necessary, which in some cases has resulted in significant acid-catalyzed decomposition of the identifier.

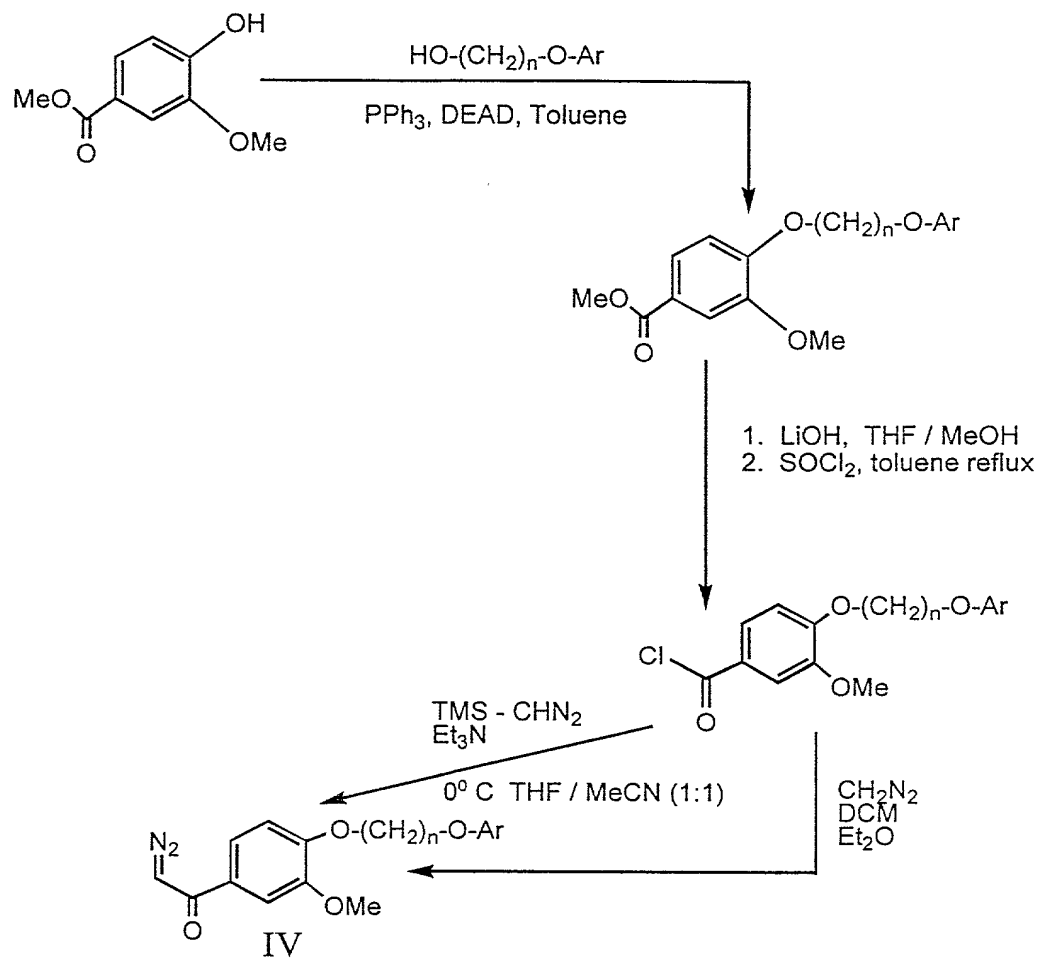
Alternate Step c). To a solution of the acid chloride (3.8 mmol, 1.00 equiv.) and 1.85 mL (13.3 mmol, 3.50 equiv.) of triethylamine in anhydrous THF/ acetonitrile (1:1) at 0°C under argon was added 5.7 mL (11.4 mmol, 3.00 equiv.) of a 2.0 M solution of (trimethylsilyl)diazomethane in hexanes. The

resulting orange solution was stirred at 0°C for 2 hr, then at 25°C for 17hr. (If a precipitate formed immediately upon addition of (trimethylsilyl)diazomethane, CH₂Cl₂ was added until the precipitate redissolved). EtOAc was added (250 mL), and the organic layer washed with saturated aq. NaHCO₃ (100 mL) and H₂O (100 mL), then dried (anhydrous MgSO₄). Removal of the volatiles in vacuo gave the product as yellow crystals in 60-100% yield.

10 The other 11 identifiers of Formula IV were prepared by analogous synthetic routes, steps (a), (b), and (c).

In the synthesis of Example 1, the 12 identifiers were used to encode the combinatorial library. In Step 1, pentachlorophenyl identifiers where n = 11-12 (abbreviated C₁₁Cl₅ and C₁₂Cl₅ were used in the following binary encoding scheme: 01 = (n=12) and 10 = (n=11). In Step 2, pentachlorophenyl identifiers where n = 8-10 (abbreviated C₈Cl₅, C₉Cl₅, and C₁₀Cl₅) were used and encoded as follows: 001 = (n=10), 010 = (n=9), and 100 = (n=8). In Step 3, pentachlorophenyl identifiers where n = 3-7 (abbreviated C₃Cl₅, C₄Cl₅, C₅Cl₅, C₆Cl₅, and C₇Cl₅) were used and encoded as follows: 00001 = (n=7), 00010 = (n=6). 00100 = (n=5), 01000 = (n=4), and 10000 = (n=3). In Step 4, trichlorophenyl identifiers where n= 5-6 (abbreviated C₅Cl₃ and C₆Cl₃) were used and encoded as follows: 01 = (n=6) and 10 = (n=5).

Thus, in Step 1 reagent 3 (Table 1-1) is encoded "11" which represents tagging this choice in the synthesis with the two pentachloro-phenyl identifiers where $n = 11$ and 12.

SCHEME 13
IDENTIFIERS

PREPARATION 2

t-BUTYL 4-(HYDROXYMETHYL)-3-NITROBENZOATE

t-Butyl 4-(acetoxymethyl)-3-nitrobenzoate was prepared as described by Barany and Albericio, *J. Am. Chem. Soc.* **1985**, 107 4936-4942. The reference's final procedure for hydrazinolysis of the acetate using hydrazine hydrate in CHCl_3 at 25°C produces only trace amounts of the desired hydroxymethyl final product, which is the t-butyl ester pre-cursor of the photocleavable linker used herein. However, hydrazinolysis using hydrazine hydrate in MeOH at 25°C produces t-butyl 4-(hydroxymethyl)-3-nitrobenzoate in high yield. Using MeOH as solvent, only the desired final product is obtained in near quantitative yield (93%).

t-butyl 4-(hydroxymethyl)-3-nitrobenzoate: To a solution of 14.1 g (47.7 mmol, 1.00 equiv.) of t-butyl 4-(acetoxymethyl)-3-nitrobenzoate in MeOH (200 mL) was added 27.0 mL (477 mmol, 10.0 equiv.) of hydrazine hydrate (55% hydrazine). The resulting yellow solution was stirred at 25°C for 4 hr. EtOAc (250 mL) and saturated aq. NaCl (85 mL) were added, and the organic layer collected after shaking. The organic layer was washed further with saturated aq. NaCl (2 x 85 mL), and then dried (MgSO_4). Removal of volatiles *in vacuo* gave the product in 93% yield as yellow crystals.

PREPARATION 3

ALLYL 4-(HYDROXYMETHYL)-3-NITROBENZOATE

In a 100 mL round bottom flask was placed 4-
5 hydroxymethyl-3-nitrobenzoic acid (1.97 g, 10 mmol).
Allyl alcohol (20 mL) was added, followed by p-
toluensesulfonic acid (0.190 g, 1 mmol). The mixture
was heated to reflux for 24 hr., at which time all
the volatiles were removed *in vacuo*. The residue was
10 taken up in EtOAc and washed with sat'd KHCO_3 . The
organic layer was dried over MgSO_4 and concentrated to
afford the title compound as a cream colored solid;
2.4 g (100%).

PREPARATION 4

15 METHYL 4-(HYDROXYMETHYL)-3-NITROBENZOATE

Following the procedure of Preparation 3, but
using methanol instead of allyl alcohol, the title
compound was prepared in 57% yield.

PREPARATION 5

20 BIS-LINKER MODIFIED RESINStep 1 Addition of bis-Boc lysine

In a 250 mL synthesis vessel was placed bis-Boc-
(L)-lysine (7.71g, 22.2 mmol) as a solution in DMF
(150 mL). HOBt (2.4g, 21.0 mmol) was added followed
25 by DIC (3.25 mL, 21.0 mmol) and the solution shaken
at r.t. for 15 min. before adding TentaGel resin
(25.8 g, approximately 7.2 mmol amino sites). The

mixture was shaken at r.t. for 17 hr and then washed alternately with methanol and DCM (5X each) and then with THF (2X) and dried under vacuum.

Step 2 Deprotection

5 Into each of seven 250 mL synthesis vessel was placed modified TentaGel resin (8.0 g, approx. 4.5 mmol of N-Boc amine sites). DCM (75 mL) was added followed by a 30% TFA solution in DCM (100 mL). The vessel was shaken at room temperature for 15 min
10 before adding neat TFA (15 mL). The vessel was shaken at room temperature for 2.5 hr at which time the resin was washed with DCM (2X). The resin was then treated with a solution of 10% triethylamine in DCM (2X150 mL) shaking for 20 min. each time. The
15 resin was then washed with DCM(4X) and DMF(1X).

PREPARATION 6

t-Boc-PROTECTED AMINO ACID

In a 1 L flask was placed 3-nitro-4-(bromomethyl) benzoic acid (20.03 g, 77.0 mmol). THF
20 (300 mL) was added followed by 4-methoxybenzylamine (10.0 mL, 77.0 mmol) and triethylamine (35 mL). The resulting clear solution was stirred at r.t. for 17.5 hr. Solid di-tert-butyl dicarbonate (16.8 g, 77.0 mmol) was added, followed by DMF (100 mL) and the
25 resulting suspension stirred at r.t. for 72 hr. The reaction mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate, washed with 1 N HCl (X2), dried (Na₂SO₄), filtered and concentrated to afford a dark brown oil. Purification via flash

chromatography (ethyl acetate:hexane) resulted in a yellow foam which was triturated with acetonitrile to give the expected protected amino acid (Table 2-1, compound 4) as a fine white powder (9.91g, 31%).

5

PREPARATION 7

t-Boc-PROTECTED AMINO ACID

Substantially following the procedure of Preparation 6, but substituting the appropriate amine for 4-methoxybenzylamine, the remaining compounds of Table 2-1 are prepared.

10

EXAMPLE 11299 COMPOUND LIBRARYStep 1a) R^1/R^2

15

To a solution of t-butyl 4-hydroxymethyl-3-nitrobenzoate (2 g, 7.89 mmol, 1 equiv.), 2,4-dihydroxyacetophenone (1.20 g, 7.89 mmol, 1 equiv.), and triphenylphosphine (2.69 g, 10.26 mmol, 1.3 equiv.) in toluene (20 mL) was added dropwise DEAD (1.79g, 10.26 mmol, 1.3 equiv.). After addition was complete the mixture was stirred for 16 hours at room temperature. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2 , eluted with 10% ethyl acetate in hexanes) affording 1.47 g of the product (48% yield).

20

25

The t-butyl ester (500 mg, 1.29 mmol, 1 equiv.) above was dissolved/suspended in DCM (8 mL) and treated with TFA (3 mL). The mixture was stirred at

room temperature for 8 hours. The DCM and TFA were removed *in vacuo* affording a white solid. This was azeotroped once with toluene then dried *in vacuo* affording 427 mg (100% yield) of the carboxylic acid.

5 The acid (636 mg, 1.92 mmol, 1.5 equiv.) prepared above was dissolved in DMF (40 mL) and added to divinylbenzene-cross-linked, polyethyleneglycol-grafted polystyrene beads (TentaGel® S NH₂, Rapp Polymere) (4.0 g, 0.32 mmol/g, 1.28 mmol, 1 equiv.)
10 in a Merrifield reaction vessel. The resin was suspended by agitation, then HOBt (259 mg, 1.92 mmol, 1.5 equiv.) and DIC (0.31 mL, 1.92 mmol, 1.5 equiv.) were added in that order. The resin was agitated at room temperature for 7 hours at which time it gave a
15 negative Kaiser test. The resin was filtered and washed (DMF 3x50 mL, DCM 3x50 mL) then dried *in vacuo*.

 The two other dihydroxyacetophenones were attached to the resin via the photocleavable linker
20 in an analogous manner using the reagents of Table 1-1.

Alternate a)

 In an analogous fashion the allyl and methyl esters were prepared from allyl 4-hydroxymethyl-3-nitrobenzoate (Preparation 3) and methyl 4-hydroxymethyl-3-nitrobenzoate (Preparation 4).

25

In a 10 mL flask was placed the allyl ester (110 mg, 0.3 mmol). Methylene chloride (2 mL) was added followed by tetrakis-triphenylphosphine palladium(0) (11.5 mg, 0.01 mmol) and the mixture cooled to 0°C. Pyrrolidine (50 mL, 0.6 mmol) was added and the reaction stirred at 0°C for 45 min. The mixture was diluted with EtOAc (10 mL) and washed with 3.5N HCl. The organic layer was dried (MgSO₄), filtered, and concentrated to afford a yellow solid; 90.6 mg.

In an analogous manner the methyl ester was deprotected by basic hydrolysis using a mixture of dilute NaOH and THF.

b) Encoding of Step 1

Quantities of the three resin batches (2.5 g) from Step 1(a) were placed in a separate synthesis vessels and each was suspended in DCM (20 mL). The three appropriate binary coding mixtures (Table 1-1) for each batch of resin were prepared by dissolving the appropriate choice (37.5 mg) or choices (37.5 mg of each) of C₁₂Cl₅ and C₁₁Cl₅ - linker diazoketone (Preparation 1) in DCM (1 mL for each solution). These solutions were added to the appropriate synthesis vessel and the resin was agitated for 30 mins.

Rhodium trifluoroacetate dimer (1 mL of a 1 mg/mL solution in DCM) was added to each of the vessels and the resin was agitated at room temperature for 4 hours. Each batch of resin was

then filtered and washed with DCM (2x20 mL) then each was resuspended in DCM (20 mL) and treated a second time with the appropriate binary encoding mixture as described above. The resin was again agitated for 30
5 mins before addition of the rhodium trifluoroacetate dimer. The same quantities of catalyst and diazoketone compounds were used in the second coupling step as in the first. The resin was agitated for 14 hours. Each resin batch was then
10 washed with DCM (5x20 mL) then the batches were combined and the entire library (three compounds) was washed with DCM (10x50 mL).

Step 2

a) Cyclocondensation Reactions

15 The dried resin from Step 1(b) was divided into four batches of 1.5 g (ca. 0.42 mmol) and three additional batches of 0.2g (ca. 0.056 mmol). The 1.5g batches were placed into 25 mL round-bottomed flasks and the 0.2 g batches were placed into 5 mL
20 round-bottomed flasks. The portions of resin were suspended in methanol (15 mL in the four flasks with 1.5 g of resin, 2 mL in the three flasks with 0.2 g of resin) and pyrrolidine (0.6 mL, 7.2 mmol, ca. 15 equiv. in the flasks with 1.5 g of the resin; 0.08
25 mL, 0.96 mmol, ca. 15 equiv. in the flasks with 0.2 g of resin) was added to each flask. The reaction vessels were then allowed to stand for 5 mn. to allow mixing of the reagents. The appropriate ketone (>10 equiv.) was then added to the vessels. The four BOC

protected aminoketones were added to the flasks containing 1.5 g of resin and the other ketones were added to the flasks containing the 0.2 g of resin. The mixtures were heated at 75°C for 16 hr. The
5 flasks were then cooled to room temperature and each batch of resin was poured into a separate sintered funnel and washed thoroughly with DMF (3x20 mL) and DCM (3x20 mL).

b) Encoding of Step 2

10 Each batch of resin from Step 2(a) was placed into a separate synthesis vessel and was suspended in DCM (5 mL for the batches of 1.5 g of resin, 1 mL for the batches containing 0.2 g of resin). The seven appropriate binary coding mixtures (see Table 1-2)
15 for each batch of resin were prepared by dissolving the appropriate choice (22.5 mg if added to a batch of 1.5 g of resin; 3.0 mg if added to a batch of 0.2 g of resin) of $C_{10}Cl_5$, C_9Cl_5 , and C_8Cl_5 linker-diazoketone (Preparation 1) in DCM (1 mL for each
20 solution). These solutions were added to the appropriate synthesis vessel and the resin was agitated for 30 mins.

Rhodium trifluoroacetate dimer (1 mL of a 1 mg/mL solution in DCM) was added to each of the
25 vessels and the resin was then filtered and washed with DCM (2x20 mL) then each was resuspended in DCM (5 mL for the batches of 1.5 g of resin, 1 mL for the batches of 0.2 g of resin) and treated a second time with the appropriate binary encoding mixture as

described above. The resin was again agitated for thirty mins before addition of the rhodium trifluoroacetate dimer. (The same quantities of catalyst and diazoketone compounds were used in the second coupling step as in the first.) The resin was then agitated for 16 hr. Each resin batch was then washed with DCM (5x20 mL). The four batches of 1.5 g of resin were combined and washed with DCM (10x50 mL). These combined batches were then reacted further in Step 3.

The three batches of 0.2 g of resin were combined and washed with DCM (10x20 mL). These combined batches were not used in Step 3 but were saved for Step 4.

15 Step 3

a) Encoding of Step 3

The four batches of 1.5 g of resin which had been combined in Step 2(b) were now divided into thirty lots of 170 mg each in 1 dram shell vials (Fisher Scientific) and each was suspended in DCM (2 mL). The thirty appropriate binary coding mixtures (see Table 1-3) for each batch of resin were prepared by dissolving the appropriate choice (3 mg) or choices of (3 mg of each) of C_7Cl_5 , C_6Cl_5 , C_5Cl_5 , C_4Cl_5 , and C_3Cl_5 linker-diazoketone (Preparation 1) in DCM (1 mL for each solution). These solutions were added to the appropriate synthesis vessel and the resin was agitated for 30 mins.

Rhodium trifluoroacetate dimer (1 mL of a 1

mg/mL solution in DCM) was added to each of the vessels and the resin was agitated at room temperature for 4 hr. The supernatant solution was then decanted away from the resin with a Pasteur
5 pipette. The resin was washed twice with DCM (3 mL) and the washing removed by Pasteur pipette. Each batch of resin was resuspended in DCM (2 mL) and treated a second time with the appropriate binary encoding mixture as described above. The resin was
10 again agitated for thirty minutes before addition of the rhodium trifluoroacetate dimer. (The same quantities of catalyst and diazoketone compounds were used in the second coupling step as in the first.) The batches of resin were then agitated for 16 hr.
15 Each resin batch was then transferred to a small Merrifield reaction vessel and washed with DCM (3x15 mL), DMF (2x15 mL), and DCM again (2x15 mL).

b) Deprotection

Each batch of resin was treated with a 50%
20 solution of TFA in DCM (6 mL:6 mL). The resin was agitated for 2 hr and then filtered and washed with DCM (3x15 mL). The resin was then treated with a 10% solution of triethylamine in DCM (1 mL:9 mL) and agitated for 10 mins. This treatment was repeated
25 once. The resin was filtered and washed with DCM (4x10 mL).

c) Addition of R⁸

To each of the first six flasks was added DCM (5

mL) and the resin was agitated for 10 mins. 2,6-Lutidine (0.11 mL, 20 equiv.) was added to each flask followed by a solution of the appropriate chloroformate (Table 1-3) in DCM (5 mL) and the resin
5 was agitated for 4 hr. Except for isopropylchloroformate (Aldrich), the chloroformates were prepared from the appropriate alcohols by treating the alcohols (0.1 g) with a solution of phosgene in toluene (5 mL of a 1.8 M solution) for 1
10 hr, then evaporating to dryness *in vacuo*, and redissolving in DCM (5 mL).

To flasks 8,9, and 10 was added ethanol (10 mL) and the appropriate isocyanate (Table 1-3) (0.1 mL, ca. 10 equiv.) and the resin was agitated for 4 hr.

15 To flasks 11, 12, and 13 was added ethanol (10 mL) and the appropriate isothiocyanate (0.1 mL, 0.1 g of the naphthalene-isothiocyanate, ca. 10 equiv.) and the resin was agitated for 4 hr.

To flasks 7 and 14-22 was added DMF (10 mL) and
20 the appropriate carboxylic acid (ca. 10 equiv.) and HOBt (0.103 g, ca. 15 equiv.). The flasks were agitated for 30 mins then DIC (0.12 mL, ca. 15 equiv.) was added to each flask and the resin was agitated for 4 hr.

25 To flask 23-30 was added to DCM (10 mL) and triethylamine (0.15 mL, ca. 15 equiv.) and the resin was agitated for 15 mins. The appropriate sulfonyl chloride (ca. 10 equiv.) was added to the reaction vessels and the resin agitated for 4 hr.

30 The flasks were filtered and the resin washed

with DCM (3x10 mL). All of the resin was combined in one large synthesis vessel and was washed with DCM (3x50 mL), DMF (3x50 mL), and DCM again (3x50 mL). The resin was dried *in vacuo*.

5 Alternative Step 3

a) Encoding of Alternative Step 3

10 The remaining 900 mg of resin from the four combined batches of 1.5 g from Step 2(b) which had not been used in Step 3 was divided into ten portions of 90 mg, and each portion placed in a separate 1 dram shell vial (Fisher Scientific). The ten appropriate binary coding mixtures (see Table 1-5) for each batch of resin were prepared by dissolving the appropriate choice (1.5 mg) or choices (1.5 mg each) of C_7Cl_5 , C_5Cl_5 , C_4Cl_5 , and C_3Cl_5 linker-diazoketone (Preparation 1) in DCM (1 mL for each solution). These solutions were added to the appropriate synthesis vessels and the resin was agitated for 30 min.

20 Rhodium trifluoroacetate dimer (1 mL of a 1 mg/mL solution in DCM) was added to each of the vessels and the resin was agitated at room temperature for 4 hr. The supernatant solution was then decanted from the resin. The resin was washed (DCM 2x3 mL) and the washing removed by Pasteur pipette. The resin was then treated a second time with solutions of the appropriate binary coding mixtures and agitated for 30 min. before the addition of the rhodium trifluoroacetate dimer. The same

25

quantities of catalyst and diazoketone compounds were used in the second coupling as in the first. The batches of resin were then agitated for 16 hr. The resin was then transferred into small Merrifield
5 synthesis vessels and washed (DCM 6x15 mL).

b) Deprotection.

Each batch of resin was treated with a solution of TFA in DCM (4 mL:4 mL). The resin was agitated for 1 hr, then filtered and washed with DCM (2x 15
10 mL). The resin was then treated with a solution of piperidine in DCM (4 mL:4 mL) and agitated for 15 min. This treatment was repeated once. Each batch of beads was washed with methanol (2x 15 mL) and DCM (4x15 mL). Flasks 1-4 were washed with THF (3x15
15 mL).

c) Heteroarylation Reactions

The resin in flasks 1-4 was suspended in THF (6 mL). Flasks 1-3 were then treated with DBU (190 μ L, ca. 40 equiv.) followed by the appropriate heteroaryl
20 chloride (ca. 20 equiv.). Flasks 1 and 2 were heated at 55°C for 16 hr. Flask 3 was heated at reflux for 16 hr. Flask 4 was treated with triethylamine (700 μ L) and the appropriate heteroaryl chloride (ca. 20 equiv.). The resin was shaken at r.t. for 16 hr.
25 Each batch of resin was then washed in THF (2x15 mL) and dried *in vacuo*.

d) Reductive Alkylations

The resin in flasks 5-10 was suspended in DMF (8mL) and the appropriate aldehyde (ca. 67 equiv.)

added. Acetic acid (160 μ L) was added to each of the
flasks followed by sodium cyanoborohydride (ca. 67
equiv.). Flasks 5, 6, 7, 9, and 10 were shaken at
r.t. for 16 hr. Flask 8 was heated to 55°C for 16
5 hr. Each batch of resin was filtered and washed with
DMF (3x15 mL). Each of the reductive alkylation
reactions was repeated under the same conditions.
The batches of resin were washed with DMF (2x15 mL),
methanol (3x15 mL), and DCM (3x15 mL). The resin was
10 then mixed, washed with DCM (2x20 mL), and dried in
vacuo.

This part of the library did not undergo further
elaboration.

Step 4

15 a) Encoding of Step 4

To the combined resin from Step 3(c) was added
45 mg of resin from each of the seven flasks from
Step 2(b) and the resin was washed and mixed
thoroughly with DCM (3x50 mL). From this mixture was
20 weighed out three portions of 800 mg of resin and
these were placed into three separate Merrifield
synthesis vessels and suspended in DCM (10 mL). The
three appropriate binary coding mixtures (see Table
1-4) for each batch of resin were prepared by
25 dissolving the appropriate choice (24 mg) or choices
(24 mg of each) of the C_6Cl_3 and C_5Cl_3 linker-
diazoketone compound in DCM (1 mL for each solution).
These solutions were added to the appropriate

synthesis vessel and the resin was agitated for 30 mins.

Rhodium trifluoroacetate dimer (1 mL of a 1 mg/mL solution in DCM) was added to each of the vessels and the resin was agitated at room temperature for 4 hr. Each batch of resin was then filtered and washed with DCM (2x20 mL) then each was resuspended in DCM (10 mL) and treated a second time with the appropriate binary encoding mixture as described above. The resin was again agitated for 30 mins before addition of the rhodium trifluoroacetate dimer. The same quantities of catalyst and diazoketone compounds were used in the second coupling step as in the first. The resin was agitated for 14 hr. Each resin batch was then washed with DCM (3x20 mL) and then filtered.

b) Carbonyl Reaction (addition of R⁶ and R⁷)

The resin in flask 1 was resuspended in DCM (6 mL) and 1,2-ethanedithiol (1 mL) and boron trifluoride etherate (1 mL) were added. The flask was shaken at room temperature for 6 hr. The resin was then washed with DCM (20 mL) and then resuspended in DCM (6 mL) and treated once more with ethanedithiol (1 mL) and boron trifluoride etherate (1 mL). The resin was agitated at room temperature for 14 hr. The resin was then filtered and washed with DCM (5x20 mL).

The resin in flask 2 was suspended in methanol (5 mL) and solid sodium borohydride (200 mg) was

added cautiously. The flask was vented and allowed to shake gently for 1 hr. The resin was filtered and resuspended in methanol and the reduction process repeated a total of 5 times at 1 hr intervals using 200 mg of sodium borohydride each time. After the final cycle the resin was washed with methanol (3x20 mL) and DCM (3x20 mL).

The resin in flask 3 was not reacted further.

The resin from the three flasks was combined and washed with DCM (5x50 mL) and then dried *in vacuo*. A portion (500 mg) of the resin was suspended in DCM (5 mL) and TFA (5 mL) and shaken for 2 hr. The resin was then treated twice with a 10% solution of triethylamine in DCM (10 mL) and washed with DCM (5x20 mL). The resin was then dried *in vacuo*.

d) Decoding Procedure

A bead was placed in a 1.13 mm diameter pyrex capillary with 2 μ L of acetonitrile. Ceric ammonium nitrate solution (2 μ L of a 0.1 M aq. solution) and hexane (3 μ L) were added and the two-phase mixture centrifuged briefly. The tube was sealed and left at 35°C for 16 hrs, then opened. The organic layer was removed by syringe and mixed with 1 μ L of N,O-bis(trimethylsilyl)acetamide. The silylated tag solution (1 μ L) was analyzed by GC with electron capture (EC) detection.

The GC analysis was performed with a Hewlett Packard 5890 plus gas chromatograph. On column injection into a 5 m, 0.32 mm retention gap connected

to a 25 m, 0.2 mm crosslinked 5% phenylmethyl
silicone column was used. The temperature program
was set at 200°C for 1 min and then increased at a
rate of 15°C/min from 200-300°C. The pressure program
5 was set at 20 psi for 1 min, then increased at 2
psi/min to 40 psi with a total run time of 10 min.
The EC detector was maintained at 400°C and the
auxiliary gas was set at 35 psi.

Table 1-1
R¹ / R² Reagents and Encoding Scheme

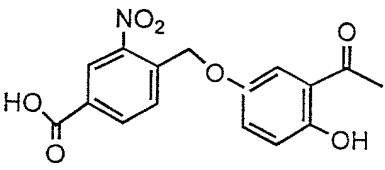
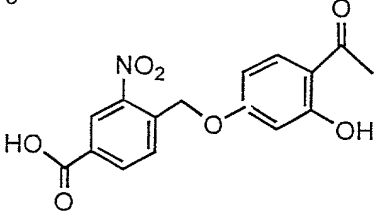
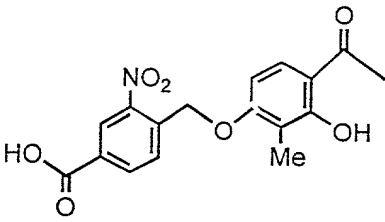
1. 01 	2. 10 
3. 11 	

Table 1-2
R⁴ / R⁵ Reagents and Encoding Scheme

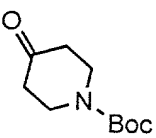
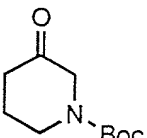
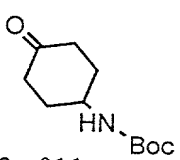
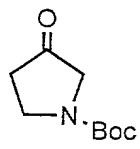
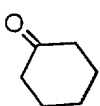
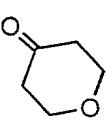
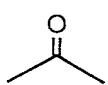
1. 001 	2. 010 	3. 011 	4. 100 
5. 101 	6. 110 	7. 111 	

Table 1-3
R⁸ Reagents and Encoding Scheme

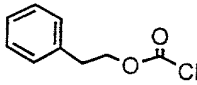
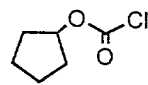
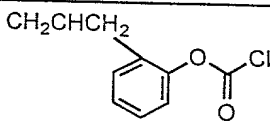
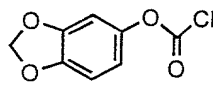
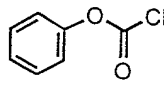
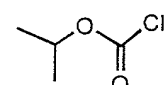
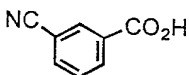
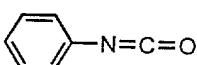
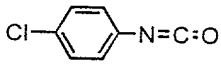
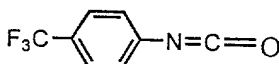
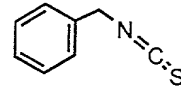
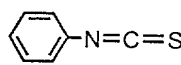
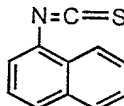
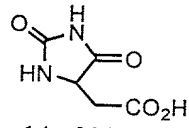
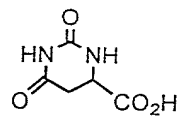
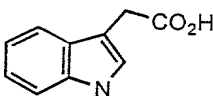
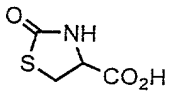
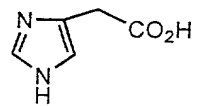
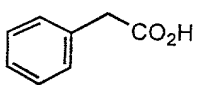
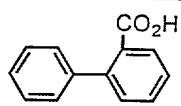
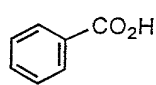
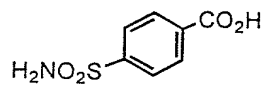
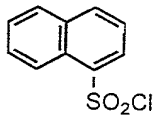
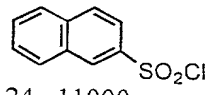
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 4. 00100	 5. 00101	 6. 00110
 7. 00111	 8. 01000	 9. 01001
 10. 01010	 11. 01011	 12. 01100
 13. 01101	 14. 01110	 16. 01111
 15. 10000	 17. 10001	 18. 10010
 19. 10011	 20. 10100	 21. 10101
 22. 10110	 23. 10111	 24. 11000

Table 1-3 con't

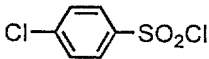
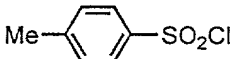
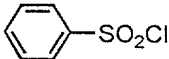
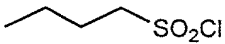
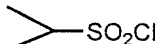
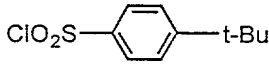
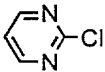
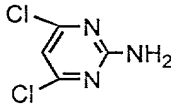
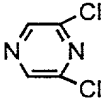
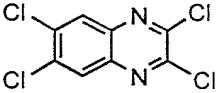
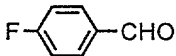
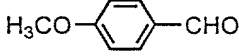
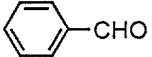
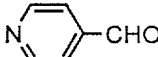

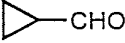
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 28. 11100	 29. 11101	 30. 11110

Table 1-4
R⁶ / R⁷ Reagents and Encoding Scheme

HS(CH ₂) ₂ SH / BF ₃ • OEt ₂ 1. 01	NaBH ₄ 2. 10	No reaction 3. 11
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Table 1-5
R¹⁴ and Heteroaryl Encoding Scheme

 1. 0001	 2. 0010
 3. 0011	 4. 0100
 5. 0101	 6. 0110
 7. 1000	 8. 1100
 9. 1010	 10. 1001

EXAMPLE 2

87,906 COMPOUND LIBRARYStep 1a) Addition of $(\text{CH}_2)_{1-6}\text{R}^{17}$

5 In a 250 mL synthesis vessel was placed the
deprotected modified TentaGel resin (8.0 g, approx.
4.5 mmol of amine sites) from Preparation 5. HOBt
(1.81 g, 13.4 mmol) was added followed by the N-Boc-
p-methoxybenzylamino acid (Table 2-1, compound 4)
10 (5.60g, 13.4 mmol) and DMF (150 mL). The mixture was
shaken at r.t. for 16 hr and then washed alternately
with methanol and DCM (4X each) and then with EtOAc
(2X). Analysis of the resin via the standard Kaiser
ninhydrin test indicated that the coupling reaction
15 was complete.

 In six separate vessels, analogous couplings
were carried out with the six other Boc-protected
amino acids listed in Table 2-1. All coupling
reactions were repeated until satisfactory Kaiser
20 ninhydrin test results were obtained (in all cases
either one or two couplings).

b) Encoding of Step 1

 While still in their separate 250 mL synthesis
vessels, resin batches number 4, 5, 6, and 7 from
25 Step 1 were suspended in EtOAc (100 mL). Into each
of these four vessels was placed the Cl_5C_7 -linker
diazoketone (0.56 g) and the mixtures agitated for 1

hr. To each of the four vessels was then added rhodium trifluoroacetate dimer (6 mL of a 1 mg/mL solution in DCM) and the resin was agitated for 15 hr. The resin was then washed with DCM (4X) and EtOAc (2X).

In turn, the Cl_5C_8 -linker diazoketone was applied to resin batches numbered 2, 3, 6, and 7.

Applications of each tagging molecule was done separately and in analogous fashion to that of the Cl_5C_7 -linker diazoketone outlined above. The seven batches of encoded resin were all combined in a 2 L Erlenmeyer flask along with THF (1 L) and mixed thoroughly by swirling and stirring gently with a glass rod. The resin was then recovered by filtration and vacuum dried.

Step 2: Addition of R^2

a) Deprotection

In a 250 mL synthesis vessel is placed mixed, encoded resin from Step 1 (9g) along with DCM (just enough to suspend resin). TFA (75 mL of a 30% solution in DCM) is added and the resin agitated for 3.5 hr. The resin is then washed with DCM (2X) followed by treatment with 10% triethylamine in DCM (2X 20 min. each) and then washed with DCM (4X).

b) Coupling

The deprotected resin from Step 2(a) (9 g) is

suspended in DMF (7 mL). HOBt (2.04 g, 45 mmol) is added followed by the acetophenone acid (Table 2-2, compound 3) (3.36 g, 15 mmol) and the mixture agitated for 15 min. DIC (2.3 mL, 15 mmol) is added and the mixture agitated for 21 hr. The resin is washed alternately with DCM and methanol (5X each) and then with EtOAc (4X).

In five separate vessels, analogous couplings are carried out with the five other acetophenone acids listed in Table 2-2.

c) Encoding of Step 2

The six batches of resin from Step 2 are binarily encoded in a fashion analogous to that described above for encoding of Step 1.

The six batches of encoded resin are combined in a 2 L Erlenmeyer flask along with THF (1 L) and mixed thoroughly by swirling and stirring gently with a glass rod. The resin is then recovered by filtration and vacuum dried.

Step 3 Addition of R^4R^5

a) Cyclocondensation reactions

The mixed resin from Step 2 is divided into three batches of 14.4 g (ca. 8.1 mmol) and seven additional batches of 1.5 g (ca. 0.84 mmol). The 14.4 g batches are placed into 250 mL round bottom flasks and the 1.5 g batches are placed in 25 mL round bottom flasks. The portions of resin are

suspended in methanol (150 mL in the three flasks with 14.4 g resin, 15 mL in the seven flasks with 1.5 g resin) and pyrrolidine (10.1 mL, 121 mmol, ca. 15 equiv. in the flasks with 14.4 g resin; 1.0 mL, 12.6 mmol, ca. 15 equiv. in the flasks with 1.5 g resin) is added to each flask. The reaction vessels are then allowed to stand for 15 min. to allow mixing of the reagents. The appropriate ketone (5 to 10 equiv.) is then added to the vessels. The three Boc-protected aminoketones from Table 2-3 are added to the flasks containing 14.4 g of resin and the seven other ketones, from Table 2-4, are added to the flasks containing 1.5 g of resin. The mixtures are heated at 75°C for 16 hr. The flasks are then cooled to r.t. and each batch of resin is poured into a separate synthesis vessel of appropriate size and washed thoroughly with DCM, DMF, and methanol (alternating: 5X each).

b) Encoding of Step 3

Each of the ten batches of resin from Step 3(a) is binarily encoded in a fashion analogous to that described for encoding Step 1.

c) Mixing and dividing

The seven 1.5 g batches of encoded resin are combined in a 500 mL Erlenmeyer flask along with THF (250 mL) and mixed thoroughly by swirling and stirring gently with a glass rod. The resin is then recovered by filtration and vacuum dried. This

combined resin is kept separate from the three 14.4 g batches of resin and is not subjected to the reaction conditions of Step 4, but rather re-divided into three 0.2 g portions and seven 1.4 g portions and saved to be used in Step 5 and alternate Step 5. The three 14.4 g batches of encoded resin are combined in a 2 L Erlenmeyer flask along with THF (1 L) and mixed thoroughly by swirling and stirring gently with a glass rod. The resin is then recovered by filtration, vacuum dried, and used in Step 4.

Step 4

a) Deprotection

Into each of seven 250 mL synthesis vessels is placed mixed, encoded resin from the three combined 14.4 g batches from Step 3 (6 g) along with DCM (just enough to suspend the resin). TFA (75 mL of a 30% solution in DCM) is added and the resin agitated for 3.5 hr. The resin is then washed with DCM (2X) followed by treatment with 10% triethylamine in DCM (2X 20 min. each) and then washed with DCM (4X).

b) Nitrogen elaboration

In the first of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, ca 3.4 mmol) is placed DCM (150 mL) and triethylamine (15 equiv.). Phenylsulfonyl chloride (ca. 10 equiv.) is added and the resin agitated for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the second of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, ca 3.4 mmol) is placed DCM (150 mL) and triethylamine (15 equiv.). Butryl chloride (ca 10 equiv.) is added and the resin agitated for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the third of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, ca. 3.4 mmol) is placed DMF (150 mL) and HOBt (ca. 15 equiv.). 4-Carboxy-benzenesulfonamide (ca 10 equiv.) is added and the resin agitated for 30 min. DIC (ca. 10 equiv.) is added and the resin agitated for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the fourth of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, ca. 3.4 mmol) is placed DMF (150 mL) and acetic acid (3 mL). Benzaldehyde (ca 50 equiv.) is added and the resin agitated for 30 min. sodium cyanoborohydride (ca 50 equiv.) is added and the resin agitated for 16 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the fifth of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, ca 3.4 mmol) is placed DMF (150 mL) and acetic acid (3 mL). Butyraldehyde (ca 50 equiv.) is added and the resin agitated for 30 min. sodium cyanoborohydride (ca 50 equiv.) is added and the

resin agitated for 16 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

5 The resin from the sixth of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6g, ca 3.4 mmol) is transferred to a 250 mL round bottom flask. THF (150 mL) is added followed by DBU (ca 40 equiv.). 2-Chloropyrimidine (ca 20 equiv.) is added. The mixture is heated to 10 55°C for 16 hr. The resin is transferred back to a 250 mL synthesis vessel, washed with alternating DCM and methanol (5X each), and then with EtOAc (2X).

In the seventh of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) 15 (6 g, ca 3.4 mmol) is placed absolute ethanol (150 mL). Methyl isocyanate (ca equiv.) is added and the resin agitated for 12 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

20 c) Encoding of Step 4

Each of the seven batches of resin from Step 4(b) are binarily encoded in a fashion analogous to that described for the encoding of Step 1.

25 The seven batches of encoded resin are combined in a 2 L Erlenmeyer flask along with THF (1 L) and mixed thoroughly by swirling and stirring gently with a glass rod. The resin is then recovered by filtration and vacuum dried. This resin is then divided into three batches of 0.7 g each and seven

batches of 5.7 g each. The seven 5.7 g. batches are subjected to Step 5. The three 0.7 g batches are subjected to alternate Step 5.

Step 5

5 a) Encoding

Each of the seven 5.7 g. batches of resin from Step 4(c) and the seven 1.4 g batches from Step 3(b) are binarily encoded in a fashion analogous to that described for the encoding of Step 1.

10 b) Reductive amination

The seven encoded 5.7 g. batches of resin from Step 5(a) are placed in 200 mL round bottom flasks. The seven encoded 1.4 g. batches from Step 3(c) are placed in 50 mL round bottom flasks. To each of the
15 fourteen flasks is added a solution of 10% glacial acetic acid in methanol (60 mL in the 200 mL flasks, 15 mL in the 50 mL flasks). The appropriate amine for Table 2-6 (ca 40 equiv.) is added followed by sodium cyanoborohydride (ca 40 equiv.). Condensers
20 are attached and the mixtures are heated to 75°C for 48 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

Alternate Step 5

a) Thioketalization

25 One of the three 0.7 g. batches of resin from Step 4(c) and one of the 0.2 batches of resin from

Step 3(c) are placed in two separate 30 mL synthesis vessels. To each is added DCM (6 mL), followed by 1,2-ethanedithiol (1 mL) and boron trifluoride etherate (1 mL). The resin is agitated at r.t. for 6
5 hr. The resin is washed with DCM (1X) and then treated once more with ethanedithiol (1 mL) and boron trifluoride etherate (1 mL). The resin is agitated at r.t. for 14 hr. The resin is then filtered and washed with alternating DCM and methanol (5X each)
10 and then with EtOAc (2X).

b) Reduction

One of the three 0.7 g. batches of resin from Step 4(c) and one of the 0.2 g batches of resin from Step 3(c) are placed in two separate 30 mL synthesis
15 vessels. To each is added methanol (6 mL) and (cautiously) solid sodium borohydride (200 mg). The flasks are vented and allowed to gently shake for 1 hr. The resin is filtered and resuspended in methanol (6 mL) and the reduction process repeated a
20 total of 5 times at 1 hr. intervals using 200 mg portions of sodium borohydride each time. After the final cycle, the resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

c)

25 One of the three 0.7 g. batches of resin from Step 4(c) and one of the 0.2 g batches of resin from Step 3(c) is left unaltered.

Step 6

a) Mixing

The seven 5.7 g batches of encoded resin from Step 5(b) are combined in a 2 L Erlenmeyer flask along with THF (1 L). The seven 1.4 g batches of encoded resin from Step 5(b) are combined in a 500 mL Erlenmeyer flask. Each batch of resin is mixed thoroughly by swirling and stirring gently with a glass rod. The resin from each flask is recovered by filtration, vacuum dried, and kept separate.

b) Nitrogen elaboration

The mixed and dried resin from the combined 5.7 g. batches in Step 6(a) (total of ca 32.5 g.) is divided into ten 3.2 g. batches and placed in 100 mL synthesis vessels. The mixed and dried resin from the combined 1.4 g. batches in Step 6(a) (total of ca 9.8 g.) is divided into ten 0.98 g. batches and placed in 30 mL synthesis vessels. These vessels are paired up into ten sets of two where each set has one 100 mL vessel and one 30 mL vessel. Both members of each set are subjected to the same reaction conditions as outlined below.

In the first set of vessels is placed N,N'-bis Boc-(L)-lysine (ca 10 equiv.) as a solution in DMF 960 mL in the larger vessel, 15 mL in the smaller). HOBt (ca 15 equiv.) is added and the resin agitated for 15 min. DIC (ca 10 equiv.) is added and the resin agitated for 4 hr. The resin is washed with DCM (2X)

and then treated with TFA (30% solution in DCM) (1.5 hrs.). The resin is then washed with DCM (2X) and treated with 10% triethylamine in DMF (2X, 30 min. each). The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the second set of vessels is placed N- α -Fmoc-N- ω -Pmc-(L)-arginine (ca 10 equiv.) as a solution in DMF (60 mL in the larger vessel, 15 mL in the smaller). HOBt (ca 15 equiv.) is added and the resin agitated for 15 min.. DIC (ca 10 equiv.) is added and the resin agitated for 4 hr. The resin is washed with DCM (2X) and then treated with TFA (50% solution in DCM) (1.5 hrs.). The resin is the washed with DCM (2X) and treated with 50% piperidine in DMF (2X, 30 min. each). The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the third set of vessels is placed DCM (60 mL in the larger vessel, 15 mL in the smaller). N,N-di-n-propyl-N'-cyano-ethylthioformamidine (ca 15 equiv.) is added, followed by triethylamine (ca 20 equiv.) and the resin agitated for 12 hrs. The resin is washed with alternating DCM and MeOH (5X each) and then with EtOAc (2X).

In the fourth set of vessels is placed absolute ethanol (60 mL in the larger vessel, 15 mL in the smaller). Methyl isocyanate (ca 15 equiv.) is added and the resin agitated for 12 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the fifth set of vessels is placed absolute

ethanol (60 mL in the larger vessel, 15 mL in the smaller). Methyl isothiocyanate (ca 15 equiv.) is added and the resin agitated for 12 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the sixth set of vessels is placed absolute ethanol (60 mL in the larger vessel, 15 mL in the smaller). Phenyl isocyanate (ca. 15 equiv.) is added and the resin agitated for 12 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the seventh set of vessels is placed absolute ethanol (60 mL in the larger vessel, 15 mL in the smaller). Phenyl isothiocyanate (ca. 15 equiv.) is added and the resin agitated for 12 hr. The resin is washed with alternating DCM and methanol 95X each) and then with EtOAc (2X).

In the eighth set of vessels is placed DCM (60 mL in the larger vessel, 15 mL in the smaller) and 2,6-lutidine (ca. 20 equiv.). Isopropyl chloroformate (ca 15 equiv.) is added and the resin agitated for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the ninth set of vessels is placed DCM (60 mL in the larger vessel, 15 mL in the smaller) and triethylamine (15 equiv.). Isobutryl chloride (ca 10 equiv.) is added and the resin agitated for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the tenth set of vessels is placed DCM (60 mL in the larger vessel, 15 mL in the smaller) and triethylamine (15 equiv.). Methanesulfonyl chloride (ca 10 equiv.) is added and the resin agitated for 4
5 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

Table 2-1
 $(\text{CH}_2)_{1-6}\text{R}^{17}$ Reagents and Encoding Scheme

<p>1.</p> <p>Cl_5C_{11}</p>	<p>5.</p> <p>Cl_5C_7 Cl_5C_{11}</p>
<p>2.</p> <p>Cl_5C_8</p>	<p>6.</p> <p>Cl_5C_7 Cl_5C_8</p>
<p>3.</p> <p>Cl_5C_8 Cl_5C_{11}</p>	<p>7.</p> <p>Cl_5C_7 Cl_5C_8 Cl_5C_{11}</p>
<p>4.</p> <p>Cl_5C_7</p>	

Table 2-2
Substituted Hydroxyacetophenone Reagents

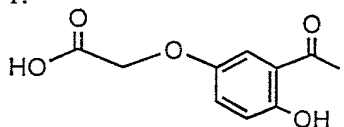
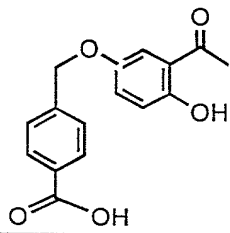
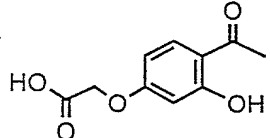
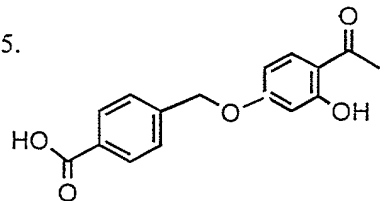
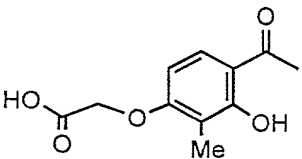
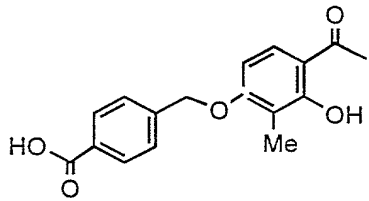
1. 	4. 
2. 	5. 
3. 	6. 

Table 2-3
R⁴R⁵ Step 3 Reagents

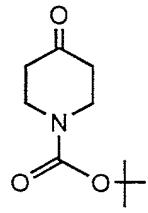
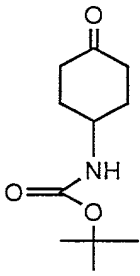
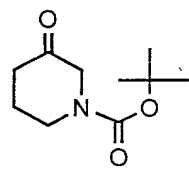
1. 	2. 	3. 
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Table 2-4
R⁴R⁵ Step 3 Alt. Reagents

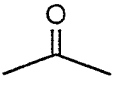
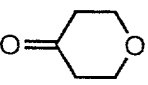
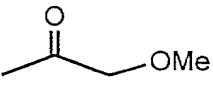
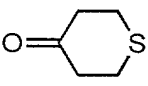
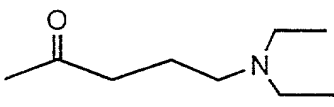
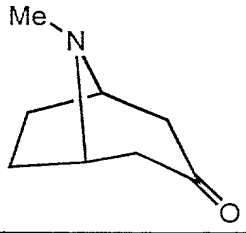
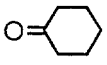
1. 	5. 
2. 	6. 
3. 	7. 
4. 	

Table 2-5
R⁸ Reagents

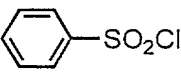
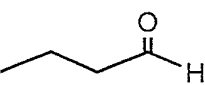
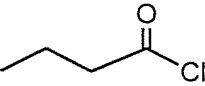
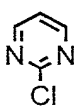
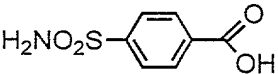
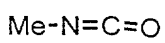
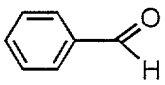
1. 	5. 
2. 	6. 
3. 	7. 
4. 	

Table 2-6
 $(\text{CH}_2)_{1-6}\text{R}^{14}$ Reagents

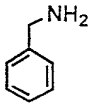
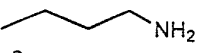
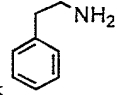
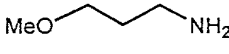
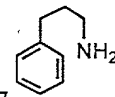
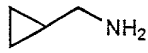
1. $\text{H}_3\text{C}-\text{NH}_2$	5. 
2. 	6. 
3. 	7. 
4. 	

Table 2-7
 R^6 / R^7 Reagents


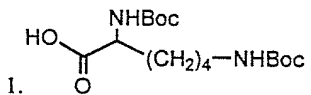
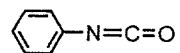
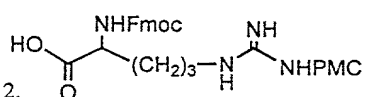
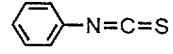
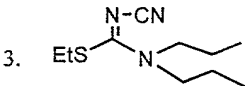
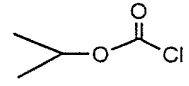
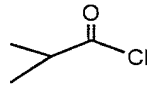
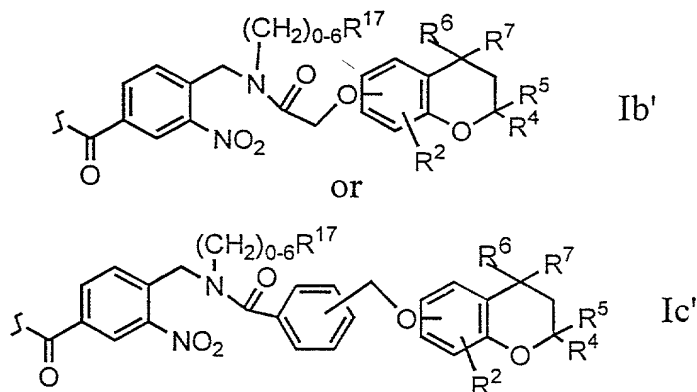
1.  BF_3OEt_2	2. NaBH_4	3. No reaction
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Table 2-8
R⁸ Reagents

1. 	6. 
2. 	7. 
3. 	8. 
4. Me-N=C=O	9. 
5. Me-N=C=S	10. Me-SO ₂ Cl

Other preferred compounds of Formula I are those of Formulae Ib' or Ic' wherein -C(O)-L'-II' is:



R¹ may also be



wherein

R¹⁸ is H or (CH₂)₀₋₅R¹⁷.

R¹⁷ may also be alkyl or substituted heterocycloalkyl. Substituted heterocycloalkyl means
 10 heterocycloalkyl substituted with loweralkyl or heteroaryl. Substituted aryl additionally means aryl substituted with loweralkyl substituted with aryl.

Scheme 12 may be modified by starting with analogs of compound 10 where R¹⁷ is bound directly to
 15 N to produce analogs 11a', 12a', and 14a where R¹⁷ is bound directly to N. Compounds of formulae 11a', 12a', 14, 14a, D, and 14' are useful as intermediates

in the construction of combinatorial libraries and are especially useful in automated or batch mode syntheses thereof.

Scheme 14

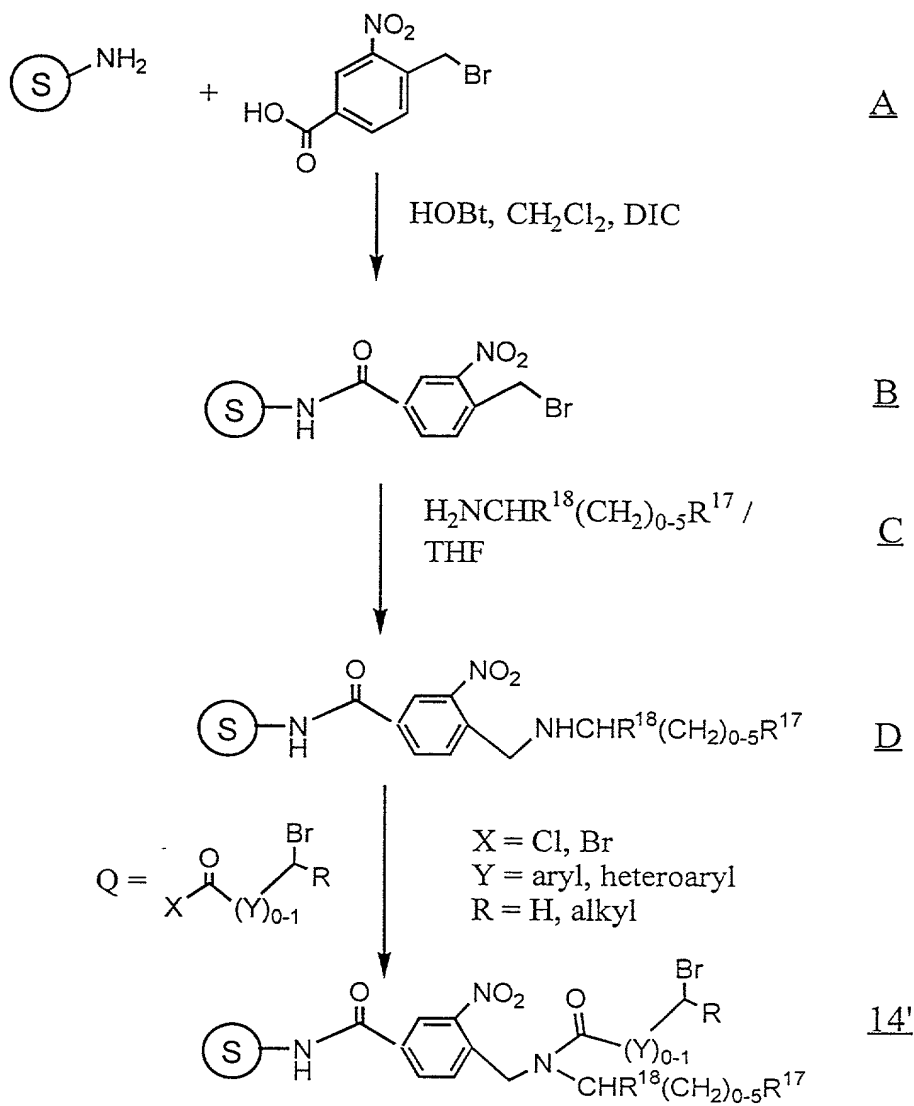
5 A process alternative to that of Scheme 12 to produce the compounds 14' is shown in Scheme 14.

Functionalized supports such as amino-functionalized or hydroxy-terminating PEG grafted polystyrene beads are placed into a reaction vessel
10 and are reacted with 3-nitro-4-bromomethylbenzoic acid (Rich and Gurwara, *Tetra.Lett*, 1975, 301), to generate benzoylamide resin B. The resin is then reacted with amine C in THF at r.t. to yield amino resin D. Amine C can be replaced by aniline or a
15 similar primary aromatic amine.

In an appropriately sized synthesis vessel is placed the amino resin D (1 equiv. of amino sites). A solvent such as DCM or DMSO is added, followed by an organic base such as triethylamine, pyridine, Hünig's
20 base (di-isopropylethylamine), or 2,6-lutidine (10 equiv.). The resin is agitated for 15 min. before adding the acid halide Q(X=Cl,Br) (5 equiv.), or an equivalent activated acid, as a dilute solution in a solvent such as DCM. The resin is agitated for 4
25 hrs. and then washed with DCM and MeOH (5X each) to yield 14'.

Photolysis of 14' as by treatment by UV at 365 nm for 2 hours yields acetamide E.

SCHEME 14
COMBINATORIAL SYNTHONS



p 153

EXAMPLE 3

Benzyl Acetamide Resin

To a solution of TentaGel® amino resin (2 g, 0.6 mmol), 3-nitro-4-bromomethylbenzoic acid (390 mg, 1.5 mmol), and HOBt (205 mg, 1.5 mmol) in 30 mL CH₂Cl₂ was added 1,3-diisopropyl-carbodiimide (250 μL, 1.5 mmol). The reaction mixture was shaken for 6-8 hr. until the Kaiser test indicated the completion of the reaction. The reagents were filtered and the resulting resin was washed (3X CH₂Cl₂, 3X CH₃OH and 3X CH₂Cl₂) and then dried to give 3-nitro-4-(bromomethyl)benzoylamide TentaGel resin.

To the above resin in 40 mL THF was added benzyl amine (1.3 mL, 12 mmol). After 8 hours shaking at room temperature, the resin was washed thoroughly (3X THF, 3X CH₃OH, and 3X CH₂Cl₂) and then dried to afford benzylamino TentaGel resin.

To the above benzylamino TentaGel resin (200 mg, 0.06 mmol) in 8 mL CH₂Cl₂ was added diisopropylethylamine (210 μL, 0.6 mmol). The reaction mixture was shaken for 2 hr. The resin was washed (3X CH₂Cl₂ and 3X CH₃OH).

EXAMPLE 4

N-Benzyl Bromoacetamide Resin

25

To benzylamino TentaGel resin, produced as in Example 3, (200 mg, 0.06 mmol) in 8 mL CH₂Cl₂ was added diisopropylethylamine (210 μL, 1.2 mmol)

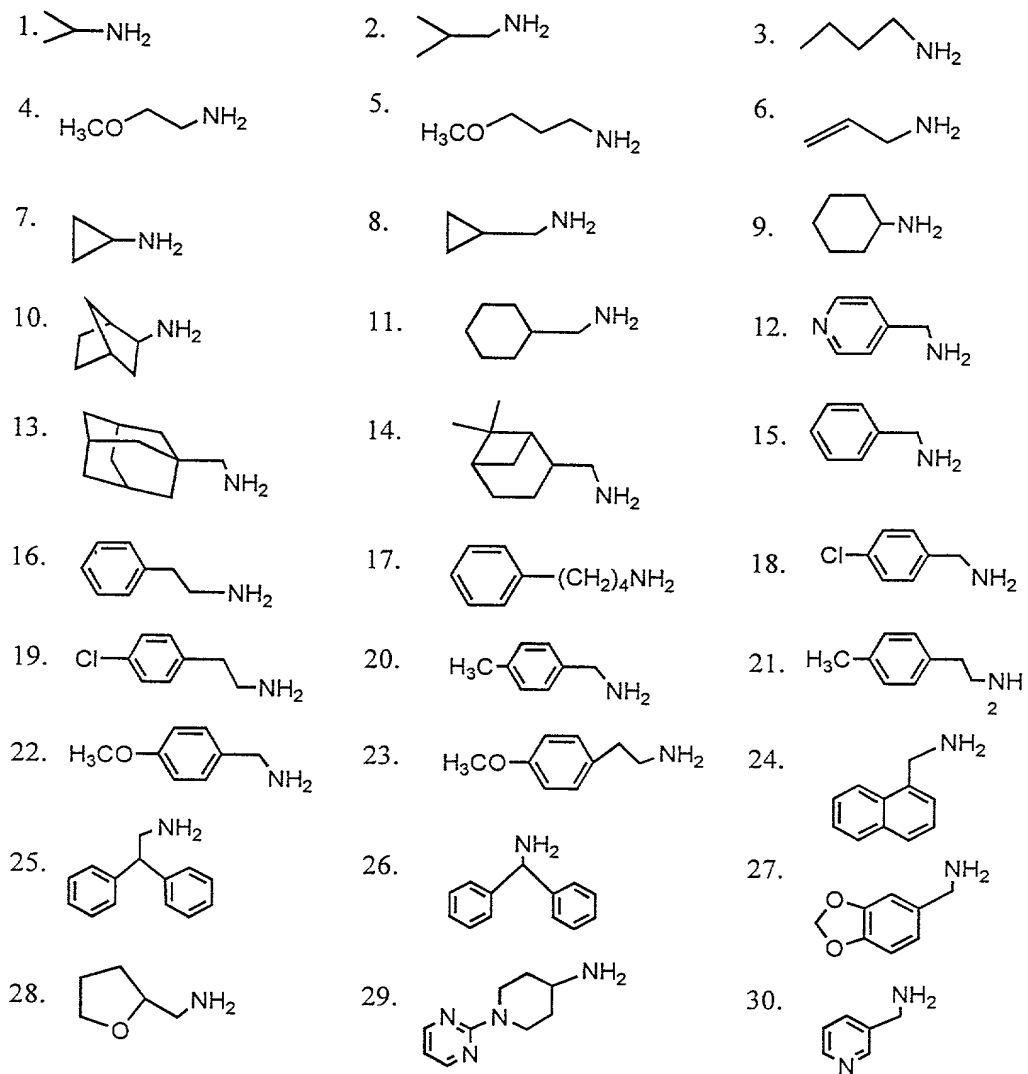
followed by bromoacetyl bromide (52 μ L, 0.6 mmol). The reaction was shaken for 2 hr. The resin was washed (3X CH_2Cl_2 and 3X CH_3OH).

EXAMPLE 5

5

Amide Synthons

Following the procedures of Examples 3 and 4 but substituting the amines of Table 5-1 for benzyl amine, analogous amides and bromoamides are produced.

Table 5-1
AMINES

EXAMPLE 6

87,906 COMPOUND LIBRARY

Following the procedure of Example 2 but
 replacing the compounds of Tables 2-3 and 2-8 therein
 5 respectively with the compounds of Tables 6-1 and
 6-2, an 87,906 compound library is produced.

Table 6-1
 R^4 / R^5 Step 3 Reagents

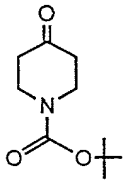
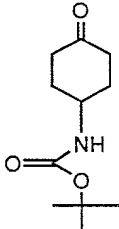
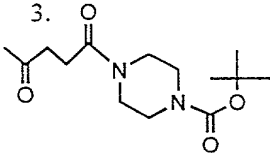
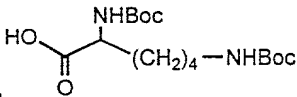
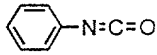
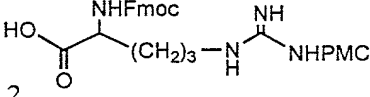
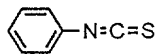
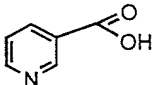
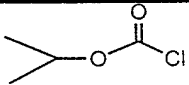
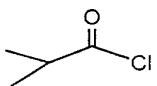
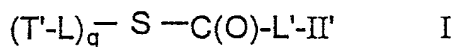
1. 	2. 	3. 
--	--	---

Table 6-2
 R^8 Reagents

1. 	6. 
2. 	7. 
3. 	8. 
4. Me-N=C=O	9. 
5. Me-N=C=S	10. $\text{Me-SO}_2\text{Cl}$

WHAT IS CLAIMED IS:

1. A combinatorial chemical library of the formula:



wherein:

(S)

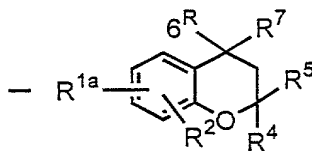
is a solid support;

T'-L- is an identifier residue;

q is 3-30;

-L'-II' is a compound/linker residue; and

-II' is of the formula:



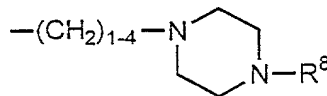
wherein:

R^{1a} is -CH₂-O-, -CH₂-CH₂-O-, -C(=O)-CH₂-O-,
-C(=O)-, or when L' terminates in
N(CH₂)₁₋₆R¹⁷, R^{1a} may additionally be
-C(=O)-Z-O- or -C(=O)-4-Phe-CH₂-O-;

R² is H or lower alkyl;

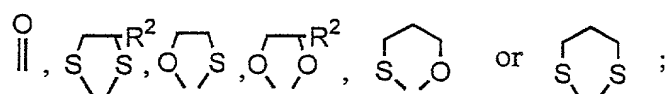
R³ is H, alkyl, aryl or arylalkyl;

R⁴ and R⁵ are each independently H, lower alkyl,
or substituted lower alkyl where the
substituents are 1-3 alkoxy, aryl,
substituted aryl, carboalkoxy, carboxamido,
diloweralkylamido, or



or R^4 and R^5 taken together are $-(CH_2)_n-$,
 $-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-O-(CH_2)_3-$,
 $-(CH_2)_2-NR^8-CH_2-$, $-CH_2-NR^8-(CH_2)_m-$,
 $-(CH_2)_2XH(NHR^8)(CH_2)_2-$, $-(CH_2)_2-S(O)_{0-2}-(CH_2)_2-$,
 or $-CH_2CH(N\text{-loweralkyl})(CH_2)_2CHCH_2-$;

one of R^6 and R^7 is H and the other is H, OH, or
 $N(CH_2)_{1-6}R^{14}R^{15}$; or R^6 and R^7 taken together are



R^8 is H, $COOR^9$, $CONHR^{10}$, $CSNHR^{11}$, COR^{12} , SO_2R^{13} ,
 lower alkyl, aryl lower alkyl, heteroaryl,
 or heteroaryl lower alkyl, wherein aryl is
 optionally substituted with 1-3
 substituents selected from lower alkyl,
 lower alkoxy, halo, CN, NH_2 , COOH, $CONH_2$,
 carboalkoxy, and mono- or di-lower
 alkylamino and wherein heteroaryl is a
 mono- or bicyclic heteroaromatic ring
 system of 5 to 10 members including 1 to 3
 heteroatoms selected from O, N, and S and
 0-3 substituents selected from halo, amino,
 cyano, lower alkyl, carboalkoxy, $CONH_2$, and
 S-lower alkyl;

R^9 is lower alkyl, aryl, aryl lower alkyl,
 heteroaryl, aryl substituted by 1-3
 substituents selected from alkyl, alkenyl,
 alkoxy, methylene dioxy, and halo, or a 5-
 to 6-membered heterocyclic ring wherein the

hetero atom is O or N, wherein heteroaryl is a heteroaromatic ring of 5 to 6 members including 1 to 2 heteroatoms selected from O, N, and S and 0-2 substituents selected from lower alkyl, dialkylamino, lower alkoxy, and halo;

R¹⁰ and R¹¹ are each independently lower alkyl, aryl, aryl loweralkyl, or aryl substituted by 1-3 substituents selected from lower alkyl, halo, alkoxy and haloalkyl;

R¹² is lower alkyl, aryl, heteroaryl, aryl lower alkyl, heteroaryl lower alkyl, a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from O, S, and N lower alkyl, or aryl substituted with 1-3 substituents selected from lower alkyl, alkoxy, halo, sulfamoyl, lower alkyl sulfamoyl, cyano, and phenyl;

R¹³ is lower alkyl, aryl or aryl substituted with 1-3 substituents selected from lower alkyl, alkoxy, halo, CN, and haloalkyl;

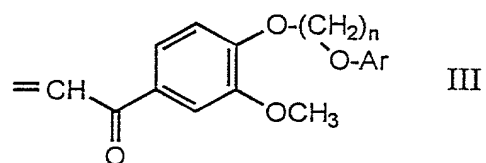
R¹⁴ is H; alkyl; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or -CH₂SC(O)R¹⁶;

R¹⁵ is H, alkyl, -C(O)X, -C(S)X, or -C(NCN)NR³R³;

- R^{16} is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;
- X is alkyl, aryl, arylalkyl, O-loweralkyl, or $-NR^3R^3$;
- Z is $-(CH_2)_{1-6}-$, optionally substituted with 1-3 lower alkyl; $-CHR^2-$; $-Phe-CH_2-$, where Phe is optionally mono-substituted with halogen, lower alkyl, or alkoxy; or heteroarylene- $(CH_2)-$;
- m is 2 or 3; and
- n is 4-9.

2. A combinatorial chemical library of Claim 1 wherein:

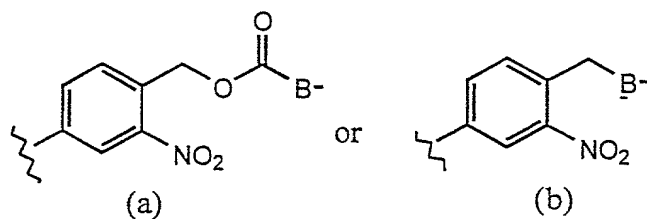
T'-L- is of the Formula:



wherein

n=3-12 when Ar is pentachlorophenyl and
 n=3-6 when Ar is 2,4,6-trichlorophenyl;
 q is 4-12; and

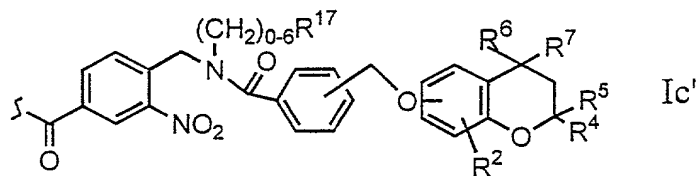
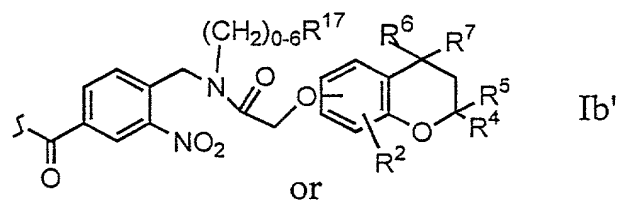
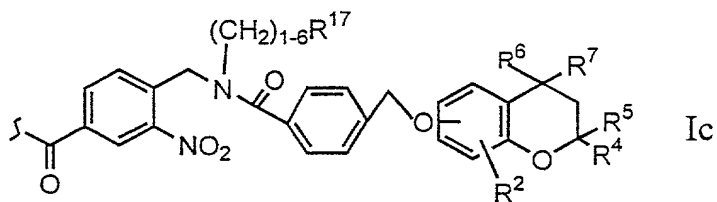
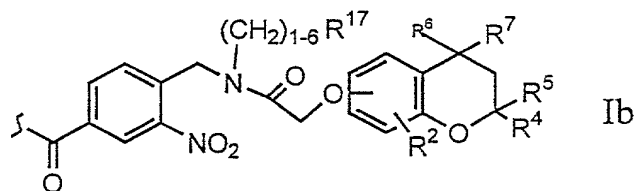
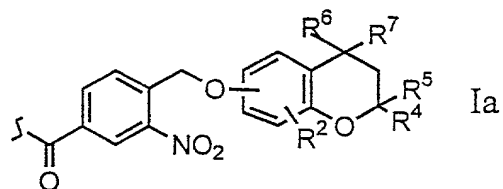
-L'- is



wherein the left-hand bond as shown is the point of attachment to the solid support and the right hand bond is the point of attachment to the compound, and B is O or N(CH₂)₁₋₆R¹⁷, with the proviso that in (b) when B is N(CH₂)₁₋₆R¹⁷, the compound is attached to B through a carbonyl group; and wherein

R¹⁷ is H; alkyl; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; substituted heterocycloalkyl; diphenylmethyl; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or -CH₂SC(O)R¹⁶.

3. A combinatorial chemical library of claim 1
wherein $-C(O)-L'-II'$ is:

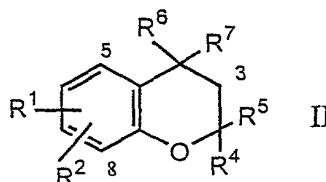


wherein:

R^{17} is H; alkyl; alkyl substituted by 1-3
alkoxy, S-loweralkyl, sulfamoyl, halo,
alkylsulphonamido, or

arylsulphonamido; alkenyl; alkynyl;
 aryl; substituted aryl; heteroaryl;
 substituted heteroaryl;
 heterocycloalkyl; substituted
 heterocycloalkyl; diphenylmethyl;
 $-\text{CH}_2\text{NR}^{16}\text{C}(\text{O})\text{R}^{16}$; $-\text{C}(\text{O})\text{NR}^{16}\text{R}^{16}$;
 $-\text{CH}_2\text{OC}(\text{O})\text{R}^{16}$; or $-\text{CH}_2\text{SC}(\text{O})\text{R}^{16}$.

4. A compound of the formula:



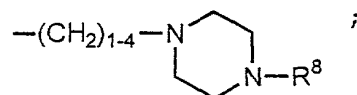
wherein:

R^1 is OH , $\text{O}(\text{CH}_2)_{1-2}\text{OH}$, $\text{OCH}_2\text{CO}_2\text{H}$, CO_2H ,
 $\text{O}-\text{Z}-\text{C}(\text{O})\text{NHCHR}^{18}(\text{CH}_2)_{0-5}\text{R}^{17}$, or
 $\text{OCH}_2-4-\text{Phe}-\text{C}(\text{O})\text{NHCHR}^{18}(\text{CH}_2)_{0-5}\text{R}^{17}$;

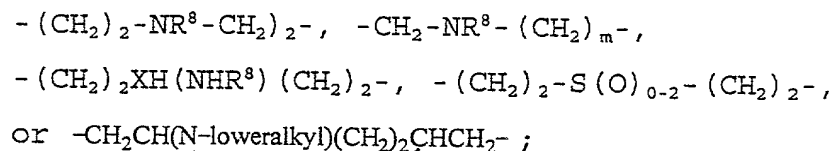
R^2 is H or lower alkyl;

R^3 is H , alkyl, aryl, or arylalkyl;

R^4 and R^5 are each independently H , lower alkyl, or
 substituted lower alkyl where the
 substituents are 1-3 alkoxy, aryl,
 substituted aryl, carboalkoxy, carboxamido,
 di-loweralkylamido, or

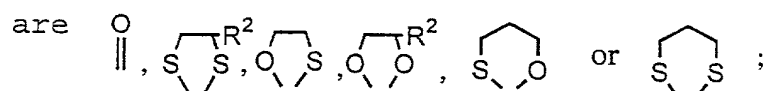


or R^4 and R^5 taken together are $-(\text{CH}_2)_n-$,
 $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$, $-\text{CH}_2-\text{O}-(\text{CH}_2)_3-$,



one of R^6 and R^7 is H and the other is H, OH, or

$\text{N}(\text{CH}_2)_{1-6}\text{R}^{14}\text{R}^{15}$; or R^6 and R^7 taken together



R^8 is H, COOR^9 , CONHR^{10} , CSNHR^{11} , COR^{12} , SO_2R^{13} , lower alkyl, aryl lower alkyl, heteroaryl, or heteroaryl lower alkyl, wherein aryl is optionally substituted with 1-3 substituents selected from lower alkyl, lower alkoxy, halo, CN, NH_2 , COOH, CONH_2 , carboalkoxy, and mono- or di-lower alkylamino and wherein heteroaryl is a mono- or bicyclic heteroaromatic ring system of 5 to 10 members including 1 to 3 heteroatoms selected from O, N, and S and 0-3 substituents selected from halo, amino, cyano, lower alkyl, carboalkoxy, CONH_2 , and S-lower alkyl;

R^9 is lower alkyl, aryl, aryl lower alkyl, heteroaryl, aryl substituted by 1-3 substituents selected from alkyl, alkenyl, alkoxy, methylene dioxy, and halo, or a 5- to 6-membered heterocyclic ring wherein the hetero atom is O or N, wherein heteroaryl is a heteroaromatic ring of 5 to 6 members

including 1 to 2 heteroatoms selected from O, N, and S and 0-2 substituents selected from lower alkyl, dialkylamino, lower alkoxy, and halo;

R¹⁰ and R¹¹ are each independently lower alkyl, aryl, aryl lower alkyl, or aryl substituted by 1-3 substituents selected from lower alkyl, halo, alkoxy and haloalkyl;

R¹² is lower alkyl, aryl, heteroaryl, aryl lower alkyl, heteroaryl lower alkyl, a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from O, S, and N lower alkyl, or aryl substituted with 1-3 substituents selected from lower alkyl, alkoxy, halo, sulfamoyl, lower alkyl sulfamoyl, cyano, and phenyl;

R¹³ is lower alkyl, aryl, or aryl substituted with 1-3 substituents selected from lower alkyl, alkoxy, halo, CN, and haloalkyl;

R¹⁴ is H; alkyl; alkyl substituted by 1-3 alkoxy, S-, loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or -CH₂SC(O)R¹⁶;

R¹⁵ is H, alkyl, -C(O)X, -C(S)X, or -C(NCN)NR³R³;

R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;

R¹⁷ is H; alkyl; alkyl substituted by 1-3 alkoxy,

S-, loweralkyl, sulfamoyl, halo,
alkylsulphonamido, or arylsulphonamido;
alkenyl; alkynyl; aryl; substituted aryl;
heteroaryl; substituted heteroaryl;
heterocycloalkyl; heterocycloalkyl;
diphenylmethyl; $-\text{CH}_2\text{NR}^{16}\text{C}(\text{O})\text{R}^{16}$; $-\text{C}(\text{O})\text{NR}^{16}\text{R}^{16}$;
 $-\text{CH}_2\text{OC}(\text{O})\text{R}^{16}$; or $-\text{CH}_2\text{SC}(\text{O})\text{R}^{16}$;

R^{18} is H or $-(\text{CH}_2)_{0-5}\text{R}^{17}$;

X is alkyl, aryl, arylalkyl, O-loweralkyl, or
 $-\text{NR}^3\text{R}^3$;

Z is $-(\text{CH}_2)_{1-6}-$, optionally substituted with 1-3
lower alkyl; $-\text{CHR}^2-$; $-\text{Phe}-\text{CH}_2-$, where Phe is
optionally mono-substituted with halogen,
lower alkyl, or alkoxy; or
heteroarylene- $(\text{CH}_2)-$;

m is 2 or 3;

n is 4-9;

or a pharmaceutically acceptable salt thereof.


5. A compound of claim 4 wherein R^{12} is
sulfamoylphenyl.

6. A compound of claim 4 wherein R^{12} is p-
sulfamoylphenyl.

7. A compound of claim 4 wherein:

R^1 is OH, $\text{OCH}_2\text{C}(\text{O})\text{NH}(\text{CH}_2)_{1-6}\text{R}^{17}$, or
 $\text{OCH}_2-4-\text{Phe}-\text{C}(\text{O})\text{NH}(\text{CH}_2)_{1-6}\text{R}^{17}$;

R^2 is H or lower alkyl;

R⁴ and R⁵ are each lower alkyl or $-(CH_2)_{14}-N$ -R⁸ ;

or R⁴ and R⁵ taken together are $-(CH_2)_5-$,
 $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-NR^8-(CH_2)_2-$,
 $-(CH_2)_2-CH(NHR^8)(CH_2)_2-$, $-(CH_2)_2-S-(CH_2)_2-$,
 or $-CH_2CH(NCH_3)(CH_2)_2CHCH_2-$;

R⁶/R⁷ are H/OH; =O, or $-S(CH_2)_2S-$;

R⁸ is H, COOR⁹, CONHR¹⁰, CSNHR¹¹, COR¹², SO₂R¹³, lower alkyl, aryl lower alkyl, heteroaryl wherein the ring members include 1 to 3 N atoms and the substituents are halo or amino, heteroaryl lower alkyl wherein heteroaryl is 6-membered and the heteroatoms are N, or aryl lower alkyl substituted with 1 substituent selected from lower alkyl, alkoxy, and halo;

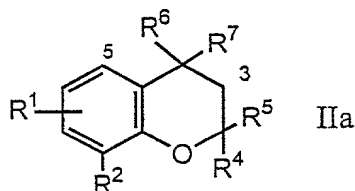
R⁹ is lower alkyl, aryl lower alkyl, aryl, tetrahydrofuranyl, tetrahydropyranyl, or aryl substituted by 1 to 2 substituents selected from lower alkyl, alkenyl, alkoxy, methylene dioxy, and halo;

R¹⁰ and R¹¹ are each independently aryl, aryl lower alkyl, or aryl substituted by 1 substituent selected from lower alkyl, halo, alkoxy, trifluoromethyl, and pentafluoroethyl;

R¹² is lower alkyl, aryl, aryl lower alkyl, heteroaryl lower alkyl wherein the heteroatoms are N, a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from S and N

lower alkyl, or aryl substituted with 1
 substituent selected from lower alkyl, alkoxy,
 halo, sulfamoyl, cyano, or phenyl;
 R^{13} is lower alkyl, aryl, or aryl substituted with 1
 substituent selected from lower alkyl, alkoxy,
 and halo;
 or a pharmaceutically acceptable salt thereof.

8. A compound of Claim 4 of the formula:



wherein:

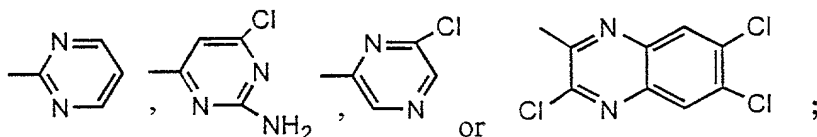
R^1 is 6- or 7-OH;

R^2 is H or lower alkyl;

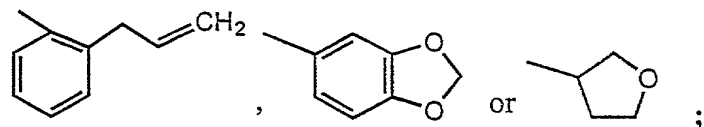
R^4 and R^5 is each methyl; or R^4 and R^5 taken together
 are $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$,
 $-(CH_2)_2-NR^8-(CH_2)_2-$, $-CH_2-NR^8-(CH_2)_3-$,
 $-CH_2-NR^8-(CH_2)_2-$, or $-(CH_2)_2-CH(NHR^8)(CH_2)_2-$;

one of R^6 and R^7 is H and the other is OH or R^6 and R^7
 taken together are $=O$ or $-S(CH_2)_2S-$;

R^8 is H, $COOR^9$, $CONHR^{10}$, $CSNHR^{11}$, COR^{12} , SO_2R^{13} ,
 benzyl, $-CH_2-Ph-4-F$, $-CH_2-Ph-4-OCH_3$,
 $-CH_2-4-Py$, n-butyl, $-CH_2-c-propyl$,



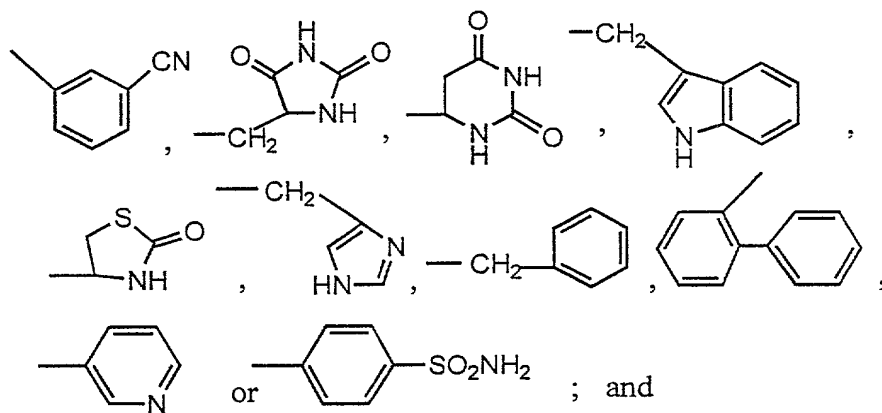
R⁹ is i-propyl, phenyl, phenethyl, t-butyl,



R¹⁰ phenyl, p-chlorophenyl, or
p-trifluoromethylphenyl;

R¹¹ is phenyl, benzyl, or 1-naphthyl;

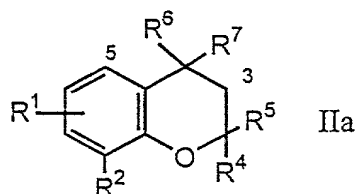
R¹² is



R¹³ is 1- or 2-naphthyl, phenyl, 4-chlorophenyl,
4-methylphenyl, 4-t-butylphenyl, n-butyl,
or i-propyl;

or a pharmaceutically acceptable salt thereof.

9. A compound of Claim 4 of the formula:



wherein:

R^1 is 6- or 7-OH when R^2 is H;

R^1 is 7-OH when R^2 is CH_3 ;

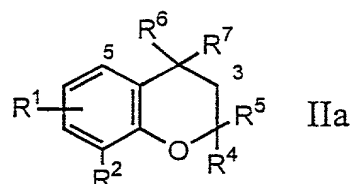
R^4 and R^5 is each methyl; or R^4 and R^5 taken together are $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-NR^8-(CH_2)_2-$, $-CH_2-NR^8-(CH_2)_3-$, $-CH_2-NR^8-(CH_2)_2-$, or $-(CH_2)_2-CH(NHR^8)(CH_2)_2-$;

one of R^6 and R^7 is H and the other is OH or R^6 and R^7 taken together are $=O$ or $-S(CH_2)_2S-$; and

R⁸ is

		or H.

10. A compound of claim 4 of the formula:



wherein:

R^1 is 6- or 7- $\text{OCH}_2\text{C}(\text{O})\text{NHCHR}^{18}(\text{CH}_2)_{0-5}\text{R}^{17}$,
 6- or 7- OCH_2 -4-Phe- $\text{C}(\text{O})\text{NHCHR}_{18}(\text{CH}_2)_{0-5}\text{R}^{17}$ when
 R_2 is H;
 R^1 is 7- $\text{OCH}_2\text{C}(\text{O})\text{NHCHR}^{18}(\text{CH}_2)_{0-5}\text{R}^{17}$, or
 7- OCH_2 -4-Phe- $\text{C}(\text{O})\text{NHCHR}_{18}(\text{CH}_2)_{0-5}\text{R}^{17}$ when R^2 is

CH₃;

R⁴ and R⁵ are each methyl; or R⁴ and R⁵ taken together

are -(CH₂)₅-, -(CH₂)₂-O-(CH₂)₂-,

-(CH₂)₂-NR⁸-(CH₂)₂-, -(CH₂)₂-CH(NHR⁸)(CH₂)₂-,

-(CH₂)₂-S-(CH₂)₂-, or $\text{-(CH}_2\text{CH(NCH}_3\text{)(CH}_2\text{)}_2\text{CHCH}_2\text{-)}$;

or R⁴ is methyl and R⁵ is -CH₂OCH₃ or

-(CH₂)₃N(Et)₂;

one of R⁶ and R⁷ is H and the other is OH; or R⁶ and R⁷

taken together are =O or -S(CH₂)₂S-; or one

of R⁶ and R⁷ is H and the other is NAB,

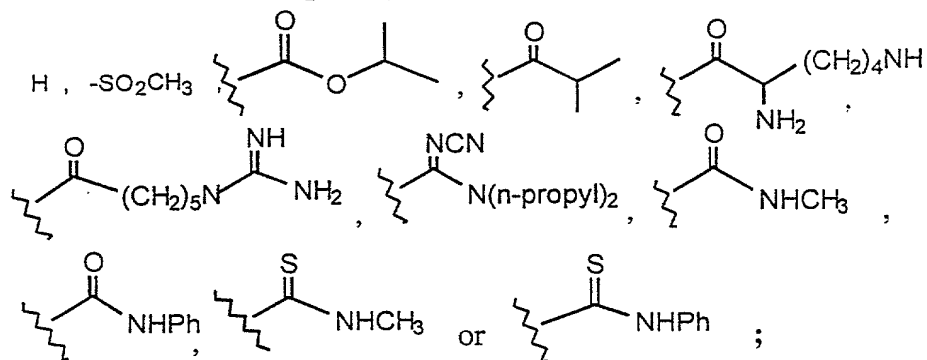
where A is methyl, 2-methoxyethyl,

2-phenylethyl, 4-methoxybenzyl,

2-tetrahydro-furanylmethyl,

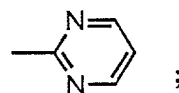
2-(3,4-dimethoxyphenyl)ethyl, or

2,2-diphenylethyl and B is



R⁸ is H, CONHCH₃, SO₂Phe, (CH₂)₃CH₃, CO(CH₂)₂CH₃,

benzyl, C(O)-(4-Phe)-SO₂NH₂, or

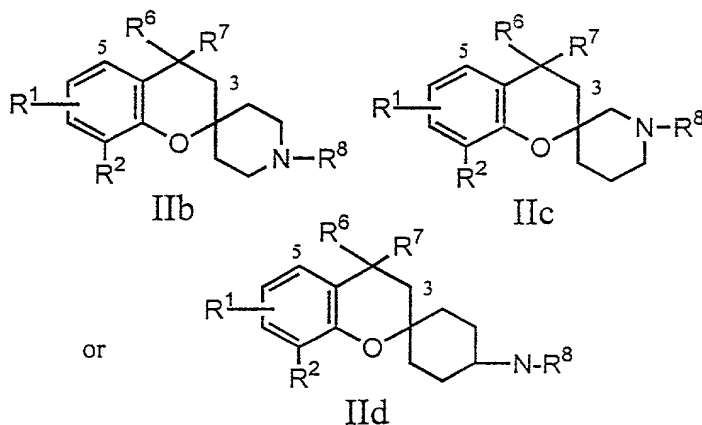


(CH₂)₁₋₆R¹⁴ is methyl, n-butyl, 3-methoxy-n-propyl,

CH₂-c-propyl, or -(CH₂)₁₋₃-phenyl; and

$(\text{CH}_2)_{1-6}\text{R}^{17}$ is methyl, 2-methoxyethyl, 2-phenylethyl, 4-methoxybenzyl, methyl-2-tetrahydrofuranyl, 2-(3,4-dimethoxyphenyl)ethyl, or 2,2-diphenylethyl; or a pharmaceutically acceptable salt thereof.

11. A compound of claim 4 of the formula IIb, IIc, or IId:



wherein:

R^1 is 6- or 7-OH, 6- or 7- $\text{OCH}_2\text{C}(\text{O})\text{NHCHR}^{18}(\text{CH}_2)_{0-5}\text{R}^{17}$, or 6- or 7- OCH_2 -4-Phe- $\text{C}(\text{O})\text{NHCHR}^{18}(\text{CH}_2)_{0-5}\text{R}^{17}$;

R^2 is H or CH_3 ;

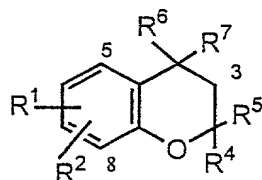
R^8 is -CO-Phe-p- SO_2NH_2 ; and

R^6 and R^7 together are =O or - $\text{SCH}_2\text{CH}_2\text{S}$ -.

12. A compound of Claim 11 wherein the substituents are as follows:

	Formula IIb	Formula IIc	Formula IIId		
R ¹	7-OH	6-OH	6-OH	6-OH	7-OH
R ²	H	H	H	H	CH ₃
R ⁶ /R ⁷	-O-	-SCH ₂ CH ₂ S-	-O-	-SCH ₂ CH ₂ S-	-SCH ₂ CH ₂ S-

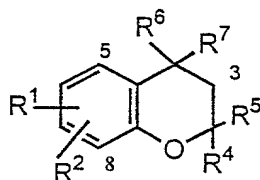
13. A compound of Claim 4 of the formula:



wherein the substituents are as follows:

R ¹	R ²	R ⁴	R ⁵	R ⁶	R ⁷
6-OH	8-CH ₃	C ₂ H ₅	C ₂ H ₅	OH	H
7-OH	8-CH ₃	CH ₃	CH ₃	H	OH
5-OH	7-C ₂ H ₅	H	CH ₂ H ₅	NH ₂	H
6-OH-(CH ₂) ₂ OH	H	C ₃ H ₇	CH ₃	=O	
7-OCH ₂ CO ₂ H	7-CH ₂ H ₅	-(CH ₂) ₄ -	H		morpholino
8-O-(CH ₂) ₂ OH	H	-(CH ₂) ₅ -	N(CH ₃) ₂		H
6-CO ₂ H	8-CH ₃	-(CH ₂) ₆ -		-S(CH ₂) ₂ S-	
6-OH	H	-(CH ₂) ₂ O(CH ₂) ₂ -		=O	
7-OH	8-CH ₃	CH ₃	CH ₃	-S(CH ₂) ₂ S-	
6-OH	H	-(CH ₂) ₅ -		=O	

14. A compound of Claim 4 of the formula:



wherein the substituents are as follows:

R ¹	R ²	R ⁴ / R ⁵	R ⁶	R ⁷	R ⁸
6-OH	H	-(CH ₂) ₂ NR ⁸ (CH ₂) ₂ -	OH	H	-CONH-Ph-4-CF ₃
7-OH	8-CH ₃	-CH ₂ NR ⁸ (CH ₂) ₃ -	-N \square SO ₂	H	-SO ₂ -2-Naph
5-O(CH ₂) ₂ OH	7-C ₂ H ₅	-(CH ₂) ₂ NR ⁸ CH ₂ -	-N \square	H	-CSNH-Ph
6-OH	H	-(CH ₂) ₂ NR ⁸ (CH ₂) ₂ -	=O		-CO-Ph-4-SO ₂ NH ₂
7-OH	H	-(CH ₂) ₂ CH(NR ⁸)(CH ₂) ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
6-OH	H	-(CH ₂) ₂ NR ⁸ (CH ₂) ₂ -	=O		-COCH ₂ Ph
6-OH	H	-(CH ₂) ₂ NR ⁸ CH ₂ -	-S(CH ₂) ₂ S-		-CO ₂ -2-Py
7-OH	8-CH ₃	-(CH ₂) ₂ NR ⁸ (CH ₂) ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
6-OH	H	-(CH ₂) ₂ NR ⁸ CH ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂

7-OH	H	$-(CH_2)_2NR^8-$ $(CH_2)_2-$	=O		-CO-Ph-4-SO ₂ NH ₂
6-OH	H	$-(CH_2)_2NR^8-$ $(CH_2)_2-$	OH	H	CONH-Ph-4-CF ₃
7-OH	8-CH ₃	$-(CH_2)_2NR^8-$ CH ₂ -	N(CH ₃) ₂	H	-SO ₂ -2-Naph
5-O(CH ₂) ₂ - OH	7-C ₂ H ₅	$-(CH_2)_2NR^8-$ CH ₂ -	-SCH ₂ CH- (CH ₃)S-	H	-CSNH-Ph
6-OH	H	$-(CH_2)_2NR^8-$ $(CH_2)_2-$	=O		-CO-Ph-4-SO ₂ NH ₂
7-OH	H	$-(CH_2)_2NR^8-$ $(CH_2)_2-$	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
6-OH	H	$-(CH_2)_2NR^8-$ $(CH_2)_2-$	=O		COCH ₂ Ph
6-OH	H	$-(CH_2)_2NR^8-$ CH ₂ -	-S(CH ₂) ₂ S-		-CO ₂ -2-Py
7-OH	8-CH ₃	$-(CH_2)_2NR^8-$ $(CH_2)_2-$	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
6-OH	H	$-(CH_2)_2NR^8-$ CH ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
7-OH	H	$-(CH_2)_2NR^8-$ $(CH_2)_2-$	=O		-CO-Ph-4-SO ₂ NH ₂

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 4 and a pharmaceutically acceptable carrier.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 9 and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 10 and a pharmaceutically acceptable carrier.

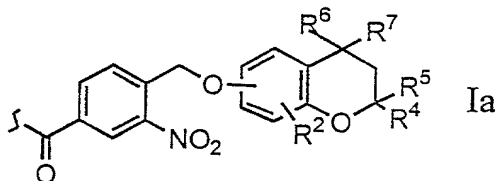
18. A pharmaceutical composition for inhibiting carbonic anhydrase in a mammal comprising a therapeutically effective amount of a compound of Claim 11 and a pharmaceutically acceptable carrier.

19. A method of inhibiting carbonic anhydrase isozymes in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 11.

20. A method of treating glaucoma in a mammal which comprises administering to a mammal in need of such treatment an effective amount of a compound of Claim 11.

21. A method of identifying a ligand having a desired characteristic which comprises synthesizing a combinatorial library of Claim 1 and testing the compounds in said library in an assay which identifies compounds having the desired characteristic.

22. A method of Claim 21 wherein the compounds in said library are those wherein $-C(O)-L''II'$ is of the formula Ia:



23. A method of Claim 21 further comprising determining the structure of any ligand so identified.

24. A method of Claim 21 wherein said characteristic is carbonic anhydrase inhibition.

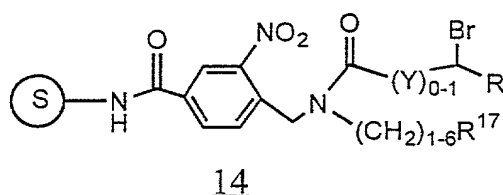
25. A method of identifying a ligand having a desired characteristic which comprises synthesizing a combinatorial library of Claim 1, detaching the ligands from the solid supports in said library, and testing said library of ligands in an assay which identifies compounds having the desired characteristic.

26. A method of Claim 25 to further comprising determining the structure of any ligand so identified.

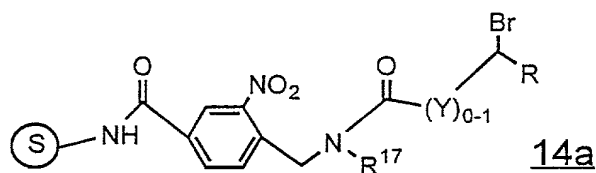
27. The use of divinylbenzene-cross-linked, polyethyleneglycol-grafted polystyrene beads as the

methylene chloride, tetrakis(triphenylphosphine) palladium(0), and pyrrolidine and stirring the mixture at 0°C, or when R is methyl reacting said compound with dilute NaOH and THF and stirring the mixture at 0°C.

30. A compound of the formula:



or



wherein:

Ⓢ is a solid support

R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;

R¹⁷ is H; alkyl; substituted heterocycloalkyl; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl;

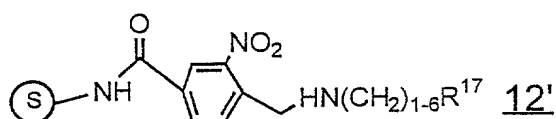
heterocycloalkyl; $-\text{CH}_2\text{SC}(\text{O})\text{R}^{16}$;

$-\text{CH}_2\text{NR}^{16}\text{C}(\text{O})\text{R}^{16}$; $-\text{C}(\text{O})\text{NR}^{16}\text{R}^{16}$; or $-\text{CH}_2\text{OC}(\text{O})\text{R}^{16}$;

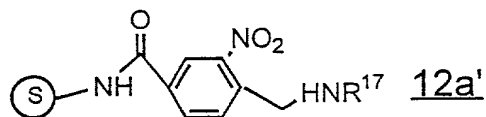
R is H or alkyl; and

Y is aryl or heteroaryl.

31. A compound of the formula:



or



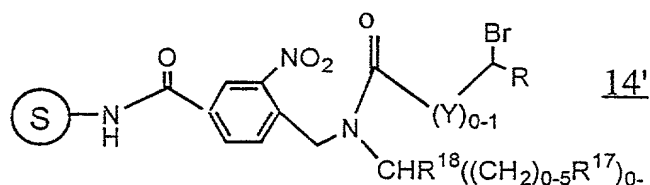
wherein:

(S) is a solid support;

R^{16} is lower alkyl, substituted lower alkyl, aryl, or substituted aryl; and

R^{17} is H; alkyl; substituted heterocycloalkyl; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; $-\text{CH}_2\text{SC}(\text{O})\text{R}^{16}$; $-\text{CH}_2\text{NR}^{16}\text{C}(\text{O})\text{R}^{16}$; $-\text{C}(\text{O})\text{NR}^{16}\text{R}^{16}$; or $-\text{CH}_2\text{OC}(\text{O})\text{R}^{16}$.

32. A compound of the formula:



wherein:

(S) is a solid support;

R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;

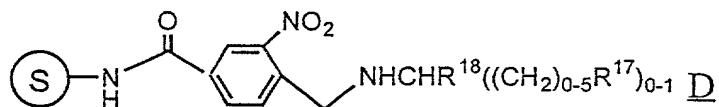
R¹⁷ is H; alkyl; substituted heterocycloalkyl; alkyl substituted by 1-3 alkoxy, S-lower alkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; substituted heterocycloalkyl -CH₂SC(O)R¹⁶; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; or -CH₂OC(O)R¹⁶;

R¹⁸ is H or (CH₂)₀₋₅R¹⁷;

R is H or alkyl; and

Y is aryl or heteroaryl.

33. A compound of the formula:



wherein:

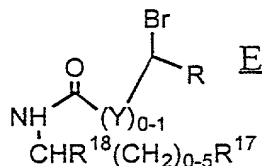
(S) is a solid support;

R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;

R¹⁷ is H; alkyl; substituted heterocycloalkyl; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; substituted heterocycloalkyl; -CH₂SC(O)R¹⁶; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; or -CH₂OC(O)R¹⁶; and

R¹⁸ is H or (CH₂)₀₋₅R¹⁷;

34. A compound of the formula:

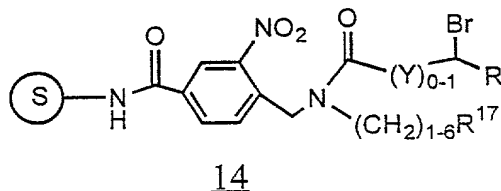
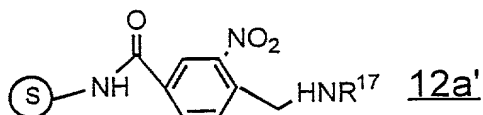
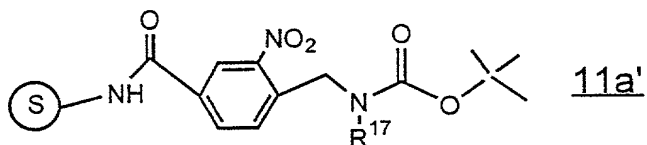


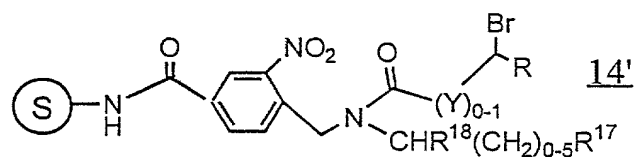
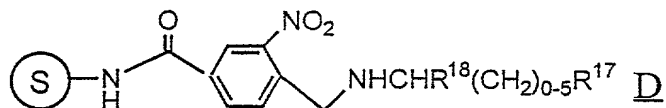
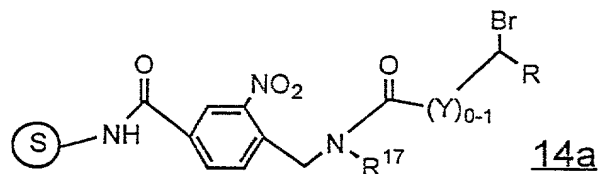
wherein:

R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;

R^{17} is H; alkyl; substituted heterocycloalkyl;
 alkyl substituted by 1-3 alkoxy,
 S-loweralkyl, sulfamoyl, halo,
 alkylsulphonamido, or arylsulphonamido;
 alkenyl; alkynyl; aryl; substituted aryl;
 heteroaryl; substituted heteroaryl;
 heterocycloalkyl; substituted
 heterocycloalkyl; $-\text{CH}_2\text{SC}(\text{O})\text{R}^{16}$;
 $-\text{CH}_2\text{NR}^{16}\text{C}(\text{O})\text{R}^{16}$; $-\text{C}(\text{O})\text{NR}^{16}\text{R}^{16}$; or $-\text{CH}_2\text{OC}(\text{O})\text{R}^{16}$;
 R^{18} is H or $(\text{CH}_2)_{0-5}\text{R}^{17}$;
 R is H or alkyl; and
 Y is aryl or heteroaryl.

35. A method of synthesizing combinatorial libraries
 which comprises the use in said syntheses of a
 compound of the formula 11a', 12a', 14, 14a, D, or
 14':

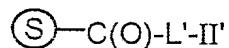




wherein:

- Ⓢ is a solid support;
- R is H or alkyl;
- R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;
- R¹⁷ is H; alkyl; substituted heterocycloalkyl; alkyl substituted by 1-3 alkoxy, S-loweralkyl; sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; diphenylmethyl, -CH₂SC(O)R¹⁶; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; or -CH₂OCOR¹⁶;
- R¹⁸ is H or (CH₂)₀₋₅R¹⁷; and
- Y is aryl or heteroaryl.

36. A combinatorial chemical library of the formula:

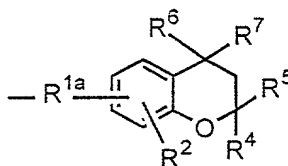


wherein:

$\textcircled{\text{S}}$ is a solid support;

$-\text{L}'-\text{II}'$ is a compound/linker residue; and

$-\text{II}'$ is of the formula:



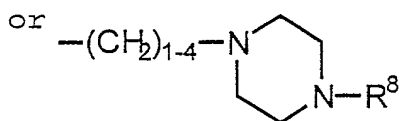
wherein:

R^{1a} is $-\text{CH}_2-\text{O}-$, $-\text{CH}_2-\text{CH}_2-\text{O}-$, $-\text{C}(=\text{O})-\text{CH}_2-\text{O}-$, $-\text{C}(=\text{O})-$,
or when L' terminates in $\text{N}(\text{CH}_2)_{1-6}\text{R}^{17}$, R^{1a} may
additionally be $-\text{C}(=\text{O})-\text{Z}-\text{O}-$ or
 $-\text{C}(=\text{O})-4\text{-Phe}-\text{CH}_2-\text{O}-$;

R^2 is H or lower alkyl;

R^3 is H, alkyl, aryl or arylalkyl;

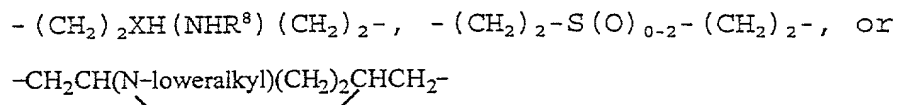
R^4 and R^5 are each independently H, lower alkyl, or
substituted lower alkyl where the substituents
are 1-3 alkoxy, aryl, substituted aryl,
carboalkoxy, carboxamido, diloweralkylamido,



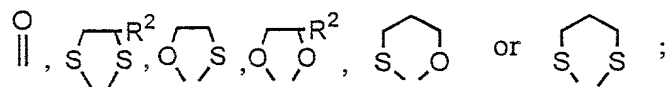
or R^4 and R^5 taken together are $-(\text{CH}_2)_n-$,

$-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$, $-\text{CH}_2-\text{O}-(\text{CH}_2)_3-$,

$-(\text{CH}_2)_2-\text{NR}^8-\text{CH}_2)_2-$, $-\text{CH}_2-\text{NR}^8-(\text{CH}_2)_m-$,



one of R^6 and R^7 is H and the other is H, OH, or $\text{N}(\text{CH}_2)_{1-6}\text{R}^{14}\text{R}^{15}$; or R^6 and R^7 taken together are



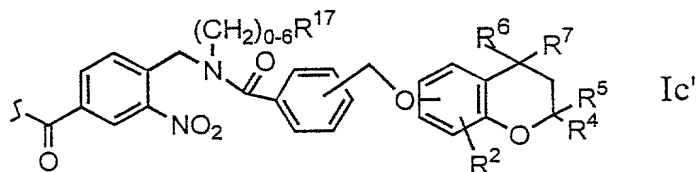
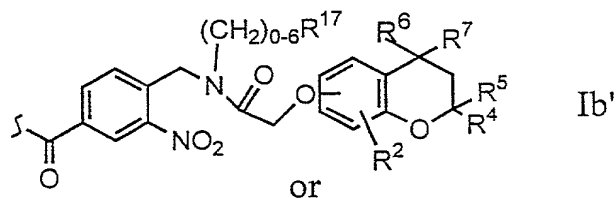
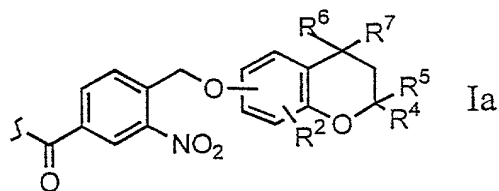
R^8 is H, COOR^9 , CONHR^{10} , CSNHR^{11} , COR^{12} , SO_2R^{13} , lower alkyl, aryl lower alkyl, heteroaryl, or heteroaryl lower alkyl, wherein aryl is optionally substituted with 1-3 substituents selected from lower alkyl, lower alkoxy, halo, CN, NH_2 , COOH, CONH_2 , carboalkoxy, and mono- or di-lower alkylamino and wherein heteroaryl is a mono- or bicyclic heteroaromatic ring system of 5 to 10 members including 1 to 3 heteroatoms selected from O, N, and S and 0-3 substituents selected from halo, amino, cyano, lower alkyl, carboalkoxy, CONH_2 , and S-lower alkyl;

R^9 is lower alkyl, aryl, aryl lower alkyl, heteroaryl, aryl substituted by 1-3 substituents selected from alkyl, alkenyl, alkoxy, methylene dioxy, and halo, or a 5- to 6-membered heterocyclic ring wherein the hetero atom is O or N, wherein heteroaryl is a heteroaromatic ring of 5 to 6 members including 1 to 2 heteroatoms selected from O, N, and S and 0-2 substituents selected from lower alkyl, dialkylamino, lower alkoxy, and halo;

- R¹⁰ and R¹¹ are each independently lower alkyl, aryl, aryl loweralkyl, or aryl substituted by 1-3 substituents selected from lower alkyl, halo, alkoxy and haloalkyl;
- R¹² is lower alkyl, aryl, heteroaryl, aryl lower alkyl, heteroaryl lower alkyl, a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from O, S, and N lower alkyl, or aryl substituted with 1-3 substituents selected from lower alkyl, alkoxy, halo, sulfamoyl, lower alkyl sulfamoyl, cyano, and phenyl;
- R¹³ is lower alkyl, aryl or aryl substituted with 1-3 substituents selected from lower alkyl, alkoxy, halo, CN, and haloalkyl;
- R¹⁴ is H; alkyl; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or -CH₂SC(O)R¹⁶;
- R¹⁵ is H, alkyl, -C(O)X, -C(S)X, or -C(NCN)NR³R³;
- R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;
- X is alkyl, aryl, arylalkyl, O-loweralkyl, or -NR³R³;
- Z is -(CH₂)₁₋₆-, optionally substituted with 1-3 lower alkyl; -CHR²-; -Phe-CH₂-, where Phe is optionally mono-substituted with halogen, lower

alkyl, or alkoxy; or heteroarylene-(CH₂)-;
 m is 2 or 3; and
 n is 4-9.

37. A combinatorial chemical library according to claim 36 wherein -C(O)-L'-II' is:



wherein:

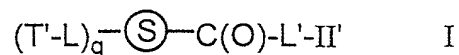
R¹⁷ is H; alkyl; alkyl substituted by 1-3 alkoxy,
 S-loweralkyl, sulfamoyl, halo,
 alkylsulphonamido, or arylsulphonamido;
 alkenyl; alkynyl; aryl; substituted aryl;
 heteroaryl; substituted heteroaryl;
 heterocycloalkyl; substituted
 heterocycloalkyl; diphenylmethyl;
 -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or
 -CH₂SC(O)R¹⁶.

TITLE OF THE INVENTION

COMBINATORIAL DIHYDROBENZOPYRAN LIBRARY

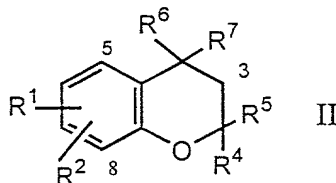
ABSTRACT OF THE DISCLOSURE

Combinatorial libraries are disclosed which are represented by Formula I:



wherein:

\textcircled{S} is a solid support; T'-L- is an identifier residue; and -L'-II' is a ligand/linker residue. These libraries contain dihydrobenzopyrans of the formula:



which interact (i.e., as agonists or antagonists) with α adrenergic receptors, dopamine receptors, δ -opiate receptors, and K^+ channels and are inhibitors of carbonic anhydrase isozymes. They are useful in the treatment of ocular diseases such as glaucoma.

Docket No.
1073.008F

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

COMBINATORIAL DIHYDROBENZOPYRAN

the specification of which

(check one)

☒ is attached hereto.

☒ was filed on _____ as United States Application No. or PCT International Application Number _____ and was amended ~~on~~ by Preliminary Amendment herewith _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

_____ (Application Serial No.)	_____ (Filing Date)
_____ (Application Serial No.)	_____ (Filing Date)
_____ (Application Serial No.)	_____ (Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

08/239,302 (Application Serial No.)	May 6, 1994 (Filing Date)	Abandoned (Status) (patented, pending, abandoned)
08/436,120 (Application Serial No.)	May 8, 1995 (Filing Date)	Pending (Status) (patented, pending, abandoned)
08/552,698 (Application Serial No.)	November 3, 1995 (Filing Date)	Pending (Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

Ronald B. Goldstein	Reg. No. 32,897	Robert E. Heslin	Reg. No. 24,778
Jeff Rothenberg	Reg. No. 26,429	Philip E. Hansen	Reg. No. 32,700
Candice J. Clement	Reg. No. 39,946	Martha L. Boden	Reg. No. 39,115

Send Correspondence to: Philip E. Hansen
Heslin & Rothenberg, P.C.
5 Columbia Circle
Albany, New York 12203

Direct Telephone Calls to: (name and telephone number)
Philip E. Hansen (518) 452-5600

Full name of sole or first inventor John J. Baldwin	
Sole or first inventor's signature <i>John J. Baldwin</i>	Date 10/11/96
Residence 621 Gypsy Hill Circle, Gwynedd Valley, PA 19437	
Citizenship United States of America	
Post Office Address 621 Gypsy Hill Circle, Gwynedd Valley, PA 19437	

Full name of second inventor, if any John C. Reader	
Second inventor's signature <i>John C. Reader</i>	Date 10/17/96
Residence 112 Biscayne Court No. 8, Princeton, NJ 08540	
Citizenship United Kingdom	
Post Office Address 112 Biscayne Court No. 8, Princeton, NJ 08540	

Full name of third inventor, if any Lawrence W. Dillard	
Third inventor's signature <i>Lawrence W. Dillard</i>	Date 10/17/96
Residence 23 East Broad Street, 3rd Floor, Hopewell, NJ 08525	
Citizenship United States of America	
Post Office Address 23 East Broad Street, 3rd Floor, Hopewell, NJ 08525	

Full name of fourth inventor, if any Ge Li	
Fourth inventor's signature <i>Ge Li</i>	Date 10/17/96
Residence 26-09 Fox Run Drive, Plainsboro, NJ 08536	
Citizenship Peoples Republic of China	
Post Office Address 26-09 Fox Run Drive, Plainsboro, NJ 08536	

Full name of fifth inventor, if any Wenguang Zeng	
Fifth inventor's signature <i>Wenguang Zeng</i>	Date 10/17/96
Residence 50 Trafalgar Court, Lawrenceville, NJ 08648	
Citizenship Peoples Republic of China	
Post Office Address 50 Trafalgar Court, Lawrenceville, NJ 08648	

Full name of sixth inventor, if any	
Sixth inventor's signature	Date
Residence	
Citizenship	
Post Office Address	